Risks of testosterone therapy in elderly men [version 1; referees: 2 approved]

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Abstract
Testosterone supplementation therapy (TST) is a widely used treatment for men with late onset hypogonadism. The benefits seen with TST, such as improved libido and energy level, beneficial effects on bone density have been well documented. Although hypogonadism remains an independent risk factor for mortality, recent studies have examined the association between testosterone therapy and cardiovascular risk.

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Vigen et al., examined the association between testosterone supplementation and cardiovascular morbidity in men older than 60 years. They performed a retrospective national cohort study of men with low testosterone levels (<300 ng/dL) who underwent coronary angiography in the Veterans Affairs (VA) system between 2005 and 2011. The absolute rate of atherosclerotic events (myocardial infarction, stroke and mortality) was 19.9% in men who did not receive testosterone vs 25.7% in the men who were treated with testosterone. Men on testosterone supplementation were reported to have higher risk of adverse events than men not on testosterone, despite being younger and having less comorbidity.

One of the most important messages to glean from the study is that hypogonadism could be an adverse prognostic factor for cardiovascular and cerebrovascular morbidity and mortality. This message is also found in other studies about hypogonadism, including a large study on male veterans that showed that hypogonadism could be an important risk factor for increased mortality. Further, in men with hypertension, low testosterone levels were shown to be associated with increased risk of major cardiovascular adverse events.

In the Vigen et al. study men who received testosterone had lower pre-therapy testosterone levels, suggesting that they were even more hypogonadal than men who did not start testosterone therapy. In addition, it is unclear how much testosterone the men in the treatment arm actually received. Based on prescription refills, most men were on testosterone therapy for less than one year, and their mean post-treatment testosterone level was 332 ng/dL. With serum testosterone less than 300 ng/dL defined as biochemical hypogonadism, we can conclude that they were even more hypogonadal, in spite of testosterone treatment.

Additionally, the reasons for starting testosterone therapy cannot be determined from this retrospective analysis. Because of the uncertain reasons for starting therapy in some hypogonadal men and not in others, and because of the variability in the amount of total testosterone that the patients actually received, there may be confounding factors that could also explain the higher risk of adverse events in men treated with testosterone. It is unclear whether the minimal exposure to testosterone in this elderly population (as evidenced by the post-treatment levels and duration of treatment) was responsible for such a dramatic difference in mortality and morbidity.

The association between testosterone therapy and mortality has remained controversial with studies demonstrating conflicting results, Until larger randomized studies demonstrate clear causation, physicians prescribing testosterone therapy to elderly men with co-morbidities should use it prudently with close follow-up.

Author contributions
RR chose the article for correspondence and evaluated the data in the manuscript. JD wrote a part of the commentary. LIL wrote the abstract and introduction. LIL supervised the process and critically edited the manuscript. All authors discussed the implications and commented on the manuscript at all stages.

Competing interests
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Version 1

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This correspondence from the Baylor group accurately summarizes many of the questions surrounding the Vigen et al. article which describes an increased cardiovascular risk profile with testosterone replacement in a highly select group of VA patients. The majority of prior studies have not detected significant increases in cardiovascular risks, except for the randomized TOM trial (Basaria et al. 2010 NEJM), which had many of its own issues with "differences detected between the two trial groups possibly...due to chance alone."

One key criticism of the Vigen et al. study, described in this correspondence, is that hypogonadism alone may portend adverse cardiovascular and cerebrovascular outcomes and that the T treatment group in this study had lower pre-treatment T values. This issue is most recently highlighted in the JCEM article by Yeap et al. from Australia in 2013 describing older Australian men with reduced mortality when testosterone was in mid-range normal levels.

Other issues with the Vigen et al. study include the heterogeneous preparations of testosterone, and varied/unknown compliance with regimens. Only 60% of patients had follow-up testosterone labs after starting therapy which is particularly important since T response differs from regimen to regimen and patient to patient. Additionally for those who had testosterone checked, were they done appropriately in the morning or at other times? Additionally, known mean post-treatment testosterone levels were barely in eugonadal range, further highlighting possible compliance issues. Certainly, additional randomized controlled trials are required to discern whether the findings in this population are generalizable to any other population.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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Dr. Ramasamy and colleagues present a well-researched brief summary on a topic which has received great attention among physicians treating low testosterone. The authors provide a nice summary of a newsworthy publication by Vigen et al. in JAMA in late 2013. The concerns presented with the methodology of this article, primarily regarding the efficacy of likely sub-therapeutic testosterone replacement therapy in an elderly veteran population, are relevant and worthy of further study. Given the conflicting studies within the literature, further research is required to clearly delineate the cardiovascular risks (or lack thereof) in elderly men receiving testosterone replacement therapy.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

**Competing Interests:** No competing interests were disclosed.