Reviewer's report

Title: Cardiovascular Risks and Elevation of Serum DHT Vary by Route of Testosterone Administration: a Systematic Review and Meta-analysis

Version: 3
Date: 21 October 2014

Reviewer: Bu Yeap

Reviewer's report:

This is a well written and carefully conducted meta-analysis.

Major compulsory revisions

1. CV events were not pre-specified endpoints in the RCTs included in the meta-analysis. Therefore in the abstract and elsewhere eg discussion, conclusions, it is more accurate to state that "Oral TRT was associated with CV adverse events", not "produced significant CV risk".

2. The reservation with this conclusion is that there were only 4 RCTs or oral T therapy. The Copenhagen study used oral micronized T, which is no longer commonly used, and treated men with alcoholic cirrhosis which currently is not an indication for T therapy. Therefore, this study should be excluded from the meta-analysis as it does not apply to current practise. The study by Chapman et al recruited men with normal T concentrations at entry (541 ng/dl) so a sensitivity analysis excluding this study would usually be appropriate. The finding of increased CV adverse events may not be robust to these exclusions.

3. The citation of ref 16 in the introduction needs to be clarified, Shores et al JCEM 2012 reported that in a cohort of veterans with lower T concentrations, those prescribed T had lower mortality compared to those who were not prescribed T. The limitations of this study have been acknowledged.

4. The authors have overlooked a large observational study which found that higher DHT concentrations were associated with lower mortality from ischaemic heart disease in older men (J Clin Endocrinol Metab. 2014 Jan;99(1):E9-18). Therefore, the hypothesis that higher DHT might contribute to CV risk is not entirely justified. A more balanced approach would be better given the contrasting observational data available. The last sentence of the abstract conclusions should be deleted, and the sections of the discussion where the contrary observational data re DHT are ignored should be amended appropriately.

5. The authors found no association of transdermal T with increased risk of CV adverse events. Therefore, the assertion that increased DHT concentrations following transdermal T therapy might contribute to risk of CV adverse events is not supported by their own analysis and should be regarded as speculative. The abstract and discussion should be moderated accordingly.
6. The section of the discussion headed "DHT elevation and increased CV risk" presents an unbalanced view of the existing published data (see comment 4 above), overinterprets the results of the meta-analysis and should be omitted completely, along with Fig 4 in its entirety. Fig 4 in particular is difficult to justify as it attempts to merge data from different studies which are not readily comparable, in which DHT is measured using different assays.

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I have received speaker honoraria and conference support from Bayer and Lilly, and am a member of a Lilly Advisory Board.