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Testosterone therapy in hypogonadal men: a systematic review and network meta-analysis

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Complete List of Authors:	Elliott, Jesse; University of Ottawa Heart Institute, Kelly, Shannon; University of Ottawa, Department of Epidemiology and Community Medicine; Ottawa Hospital Research Institute, Medicine Millar, Adam; Mount Sinai Hospital, University of Toronto Peterson, Joan; Clinical Epidemiology Program, Ottawa Hospital Research Institute Chen, Li; University of Ottawa Heart Institute, Johnston, Amy; Cardiovascular Research Methods Centre, University of Ottawa Heart Institute Kotb, Ahmed; University of Ottawa Heart Institute, Skidmore, Becky; Independent Information Specialist Mamdani, Muhammad; St Michael's Hospital, Li Ka Shing Knowledge Institute Wells, George ; University of Ottawa Heart Institute, Department of Epidemiology and Community Medicine
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Jesse Elliott, Shannon Kelly, Adam Millar, Joan Peterson, Li Chen, Amy Johnston, Ahmed Kotb, Becky Skidmore, Muhammad Mamdani, George A Wells

Jesse Elliott MSc,
Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, 40 Ruskin Street, Ottawa, Ontario, K1Y4W7

Shannon Kelly MSc,
Cardiovascular Research Methods Centre, University of Ottawa Heart Institute,
40 Ruskin Street, Ottawa, Ontario, K1Y4W7

Adam C. Millar MD MScCH
Department of Medicine, Mount Sinai Hospital, University of Toronto, Toronto, Ontario

Joan Peterson BSc,
Clinical Epidemiology Program, Ottawa Hospital Research Institute, 1053 Carling Avenue, Ottawa, Ontario, K1Y 4E9

Li Chen MSc,
Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, 40 Ruskin Street, Ottawa, Ontario, K1Y4W7

Amy Johnston MSc,
Cardiovascular Research Methods Centre, University of Ottawa Heart Institute,
40 Ruskin Street, Ottawa, Ontario K1Y4W7

Ahmed Kotb MSc,
Royal College of Surgeons in Ireland, 123 St. Stephen's Green, Dublin, Ireland

Becky Skidmore MLS,
Independent Information Specialist, Ottawa, Ontario, K1T 3Z2

Muhammad Mamdani PharmD,
Li Ka Shing Knowledge Institute, St. Michael's Hospital; Toronto, Ontario M5B1W8

George A. Wells PhD, Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, 40 Ruskin Street, Ottawa, Ontario, K1Y4W7

Correspondence to: GA Wells, gawells@ottawaheart.ca

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Contributors: JE, SK, MM, and GW designed the study. BS developed and executed the search strategy. JE, SK, JP, AJ, and AK selected studies for inclusion and extracted data. JE, AK, and LC analyzed the data. JE, SK, LC, AM, and GW interpreted the data. JE wrote the first draft of the manuscript, which was critically revised for intellectual content by all authors. All authors approved the final version submitted for publication and agree to be accountable for all aspects of the study.

Keywords: testosterone, benefits, depression, quality of life, erectile function, libido, harms, cardiovascular-related adverse events, systematic review, network meta-analysis

ABSTRACT

Objective: To assess the relative effects of individual testosterone products, most of which have never been compared head-to-head.

Design: Systematic review and network meta-analysis

Data sources: MEDLINE, Embase, Cochrane CENTRAL, and grey literature (up to October 13, 2015).

Eligibility criteria for selecting studies: Randomized controlled trials (RCTs) and non-randomized studies were selected if they involved adult hypogonadal men who received any testosterone product for at least 3 months. Eligible comparators were placebo, another testosterone product, or the same product at a different dose.

Data extraction: Data were extracted by one reviewer and checked by a second. The primary outcomes were benefits (improvements in quality of life, depression, libido, erectile function, activities of daily living, testosterone levels) and harms (cardiovascular death, myocardial infarction, stroke, prostate cancer, heart disease, diabetes, serious adverse events, withdrawals due to adverse events, erythrocytosis). Data were pooled for RCTs via meta-analysis and network meta-analysis.

Results: 73 RCTs and 41 NRS were included. Most were at high or unclear risk of bias. When compared as a class against placebo, testosterone improved quality of life and libido with no significant effect on depression or erectile function. Via network meta-analysis, we found that few individual products had a significant effect compared with placebo, and there were few significant differences among the treatments for any beneficial outcome. We found no increased risk of any harm, including cardiovascular-related adverse events, with the exception of withdrawals due to adverse events; however, most included trials were of short duration and at high risk of bias.

Conclusion: Despite a class effect of improving quality of life and libido, major improvements were not observed for any individual product. We observed no statistically significant increase in any major harm; however, longer-term high-quality trials are needed to fully assess the risk of adverse outcomes.

Registration: PROSPERO CRD42014009963

Article Summary

Strengths and limitations

- We performed a comprehensive systematic review of the published and grey literature to identify randomized and non-randomized studies involving adult men with low testosterone levels
- Although there is no universally agreed on level for the diagnosis of "low" testosterone, we included only studies that enrolled men with total testosterone ≤ 12 nmol or free testosterone ≤ 225 pmol/L, consistent with recent guidelines.
- Data in non-randomized studies were poorly reported and were not suitable to pooling via meta-analysis.
- The included studies were generally at high or unclear risk of bias, and most studies had a relatively short treatment duration.
- Long-term high-quality studies are needed to more fully assess the risk of rare adverse events.

Introduction

Testosterone deficiency has well-recognized negative effects on male sexuality and quality of life.[1] Recent clinical practice guidelines recommend testosterone therapy for adult men with low testosterone levels (hypogonadal men) with the goal of improving symptoms and elevating testosterone levels into the mid-normal range for young men.[2] However, two large observational studies have reported an increased risk of cardiovascular events with testosterone use,[3,4] and the US Food and Drug Administration (FDA) and Health Canada both have warned of a potential increased risk of cardiovascular events among men using testosterone products.[5,6]

Previous meta-analyses have reported positive effects of testosterone replacement therapy (TRT), compared with placebo, on quality of life,[7] depression,[8,9] and some aspects of sexual function.[10] However, the results of individual trials have been mixed, and there is variation in testosterone formulations and dose.[11] Similarly, previous meta-analyses of potential harms related to TRT have reported contradictory findings.[12–16] A 2013 meta-analysis reported an increased risk of cardiovascular-related events in a mixed population of hypogonadal and eugonadal men[15]; however, others have found no increased risk of cardiovascular outcomes, including myocardial infarction, stroke, or cardiovascular death.[12–14,16]

Because each TRT product has a different formulation and many different dosing strategies exist,[17] it may not be appropriate to group together all testosterone products, as in traditional meta-analyses. In this study, we performed a systematic review to identify randomized and non-randomized studies (NRS) involving hypogonadal men, and we used network meta-analysis to compare the relative benefits and harms of each product.

Methods

This review was registered *a priori* (CRD42014009963) and followed the Cochrane handbook[18] and the PRISMA for Network Meta-Analysis checklist.[19] Our review included randomized controlled trials (RCTs) and NRS involving men with low testosterone taking any form of testosterone replacement

therapy compared to placebo, another testosterone product, or the same product at a different dose. We did not exclude studies on the basis of outcomes reported in the individual studies.

Patient involvement: No patients were involved in setting the research question or in developing plans for design, or implementation of the study. A patient representative was involved in selecting the outcome measures, and patient groups were given the opportunity to comment on the study protocol. No patients were asked to advise on the interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Search strategy: We searched Ovid MEDLINE, Ovid MEDLINE In-Process & Other Non-Indexed Citations, and Embase Classic+Embase, and Cochrane CENTRAL (up to June 8, 2014; eAppendix 1); grey literature were searched according to CADTH's Grey Matters Light.[20] The search was updated on October 13, 2015.

Study selection: We included placebo- and active-controlled RCTs and NRS involving adult men (≥ 18 yr) with low testosterone (total testosterone ≤ 12 nmol/L or free testosterone < 225 pmol/L) taking a testosterone product. We excluded studies that artificially suppressed endogenous testosterone, involved testosterone precursors, or had less than 10 participants. We included studies with a treatment duration of 12 weeks or longer, as follow-up is generally recommended for this time point.[2,21] Cross-over trials were included if the initial period was at least 12 weeks. Titles and abstracts were screened in duplicate (JE, JP), and the full-text of any potentially relevant record was evaluated (JE, JP, AJ). Disagreements were resolved by consensus.

Data extraction and risk of bias: Data were extracted by one reviewer using piloted standardized abstraction forms (Distiller SR) and checked by a second reviewer (JE, JP, AJ, AK). Data from RCTs were included for benefits outcomes, and data from RCTs and NRS were included for harms outcomes. First-period data were extracted from cross-over trials. Risk of bias was assessed by two reviewers using

the Cochrane Collaboration's risk of bias tool for RCTs or SIGN50 for cohort studies. Disagreements were resolved by discussion. Publication bias was assessed by visual inspection of funnel plots.

Outcomes: Outcomes were grouped as benefits (quality of life, depression, libido, erectile function, and activities of daily living, testosterone level at 3 mo, 6 mo, end of study) and harms (cardiovascular death, myocardial infarction, stroke, prostate cancer, diabetes, heart disease, serious adverse events, withdrawals due to adverse events, erythrocytosis). We included data for quality of life, depression, erectile function, and libido that had been measured using a validated scale (a complete list of scales is available from the corresponding author).

Data analysis*:* The results of the included NRS are summarized narratively. Meta-analysis and network meta-analysis involving data from RCTs were performed as described below. We performed meta-analysis using RevMan (v.5.3; Cochrane Collaboration) and Bayesian network meta-analysis using WinBUGS (v.1.4.3; MRC Biostatistics Unit). The number randomized was used as the denominator for benefits outcomes, and the number who received treatment was used for harms. Two trials[22,23] were removed from the analyses because the data from these trials were outliers for each outcome and each had a considerable effect on heterogeneity. For example, removal of the trial by Cavallini and colleagues reduced the I^2 value from 81% to 11% for the outcome erectile function. In an exploratory analysis, we removed trials enrolling men with major comorbidities (i.e., HIV/AIDS, osteoporosis, metabolic syndrome, type 2 diabetes, angina, Alzheimer's disease, heart failure, end-stage renal disease).

In the network meta-analysis, we used a binomial likelihood model for dichotomous outcomes and a normal likelihood model for continuous outcomes, allowing for the inclusion of multi-arm trials.[24] Network meta-analyses included all trials that reported each outcome with no restriction based on comorbidities. Each dose of an individual testosterone product was included as a separate node. A continuity correction was applied to adjust zero events for harm outcomes. Assessment of model fit and choice of model (fixed v. random effects) was based on assessment of the deviance information criterion

and comparison of residual deviance to the number of unconstrained data points.[24] Results are reported for the random-effects model. We derived point estimates and 95% credible intervals (CrIs) using the Markov Chain Monte Carlo method. Mean differences, standardized mean differences with standard deviations (SDs) or odds ratios (ORs) with 95% CrIs are reported for continuous or dichotomous outcomes. Vague priors (e.g., N[0, 100^2]) were assigned for basic parameters throughout.[24] To ensure model convergence, trace plots and Brooks-Gelman-Rubin statistics were assessed.[25] Three chains were fit for each analysis with at least 20,000 iterations and a burn-in of at least 20,000 iterations. Inconsistency was assessed where possible by comparing the deviance, between-study variance, and deviance information criterion statistics of the consistency and inconsistency models.[26] The posterior mean deviance of the individual data points in the inconsistency model was plotted against the posterior mean deviance in the consistency model.[26] All network diagrams were constructed using NodeXL.

Role of the funding source: The funder had no role in study design, data collection, analysis, interpretation, or writing. All authors had full access to the study data, and the corresponding author had final responsibility for the decision to submit for publication.

Results

Search results and study characteristics

We identified 72 RCTs and 41 NRS published between 1997 and 2014 (Figure 1, eAppendix 2). Of these, 57 RCTs and 11 NRS reported an outcome of interest (eTable1,2). The median duration of RCTs was 6 months (range: 3–36 mo), with mean participant age ranging between 30 and 78 years (eTable1). Most RCTs were placebo controlled (84%), with 2 treatment groups (86%). Of the included NRS, 6 were retrospective and 5 were prospective cohorts, with a duration between 2 and 36 months (eTable2). Few RCTs or NRS were at low risk of bias, primarily because of a lack of details about randomization procedures, allocation concealment, and analysis populations (eTable3,4).

Consistency

Comparison of the consistency and inconsistency models for libido and total testosterone levels did not show evidence of inconsistency (eAppendix5). Consistency could not be evaluated for quality of life, depression, or erectile function because of a lack of closed loops.

Benefits

Quality of life: In total, 18 placebo-controlled RCTs involving 2698 participants assessed quality of life. Compared with placebo, treatment with any TRT significantly improved quality of life (standardized mean difference [SMD] –0.23, 95%CI –0.38,–0.09) with substantial heterogeneity (I^2 = 62%; Figure 2A). To explore this heterogeneity, we excluded RCTs that involved men with major comorbidities. This reduced heterogeneity into the moderate range (I^2 = 45%), with little effect on the point estimate (SMD –0.43, 95%CI –0.76,–0.09; Figure 2B).

The evidence network for quality of life comprised 20 RCTs, representing 14 treatments in addition to placebo (n = 2698). Figure 3 shows the evidence network for quality of life; networks for the other outcomes are shown in eAppendix4. Compared to placebo, no treatment significantly improved quality of life, and there were no significant differences among the treatments (Table 1). The results were consistent when only studies with no major comorbidities were included (data not shown).

Depression: 11 trials involving 842 participants randomized to 9 treatments evaluated depression. Compared with placebo, treatment with any TRT had no significant effect on depression (SMD –0.18, 95%CI –0.49,0.13); however, heterogeneity was substantial (I^2 = 73%) (eFigure2A). Removal of trials involving men with major comorbidities did not resolve this heterogeneity (I^2 = 81%; SMD –0.35, 95%CI –0.95,0.25) (eFigure2B).

In the network meta-analysis, intramuscular testosterone enanthate (200 mg/2wk) was significantly better than placebo at improving symptoms of depression (eTable 5). Among the treatments, intramuscular

testosterone enanthate (200 mg/2wk) was significantly better than intramuscular testosterone enanthate administered as 125 mg/wk and Sustanon (100 mg/2 wk). When trials involving men with major comorbidities were removed, there were no significant differences compared with placebo or among the treatments (data not shown).

Libido: 9 trials involving 1546 patients randomized to 7 treatments investigated libido. Compared with placebo, testosterone significantly improved libido (SMD 0.17, 95%CI 0.01,0.34; I^2 = 34%) (eFigure3A). Removal of trials involving men with major comorbidities increased heterogeneity, and the point estimate was no longer significant (SMD 0.04, 95%CI –0.28,0.36) (eFigure3B).

In the network meta-analysis, 1% gel (100 mg/d) was significantly better than placebo at improving libido. Among the treatments, 1% gel (100 mg/d) was significantly better than patch (5 mg/d) and oral testosterone undecanoate (160 mg/d). Oral testosterone undecanoate at 120 mg/d and intramuscular testosterone undecanoate (1000 mg/12 wk) were both significantly better than oral testosterone undecanoate at 160 mg/d (eTable6)

Erectile function: 11 trials involving 1226 patients randomized to 5 treatments evaluated erectile function. Compared with placebo, testosterone had no significant effect on erectile function (SMD 0.15, 95%CI –0.00,0.31), with moderate heterogeneity (I^2 = 74%; eFigure4A). Removing trials involving men with major comorbidities reduced heterogeneity (I^2 = 11%), with little change to the point estimate (SMD 0.19, 95%CI –0.03,0.40;eFigure4C).

In the network meta-analysis, there were no significant differences in erectile function for any individual testosterone product compared with placebo or among the products (eTable7). Removal of trials involving major comorbidities did not alter the results (data not shown).

Testosterone levels

In total, 23 and 19 RCTs reported T levels after 3 or 6 months of treatment, respectively. End of treatment values were reported in 47 RCTs. After 3 or 6 months of treatment, about half of the treatments in each network were associated with significantly higher total testosterone levels compared with placebo (3 mo: 6/15; 6 mo: 8/17) (eTables 8,9). By the end of treatment (12 wk to 36 mo), most products were associated with total testosterone above 12 nmol/L (20/25 testosterone therapies), and 11 of 25 treatments had significantly higher levels relative to placebo (eTable10). Intramuscular testosterone enanthate was associated with significantly higher testosterone levels compared with most other products at the end of treatment.

Harms

Cardiovascular death: 8 RCTs reported the occurrence of cardiovascular death during the treatment period, while an additional 7 trials reported no CV deaths. Compared with placebo via pair wise meta-analysis, there was no significant difference between groups in the risk of cardiovascular death (OR 2.49, 95% CI 0.75,8.21; I^2 = 10%) (eFigure5). In the network meta-analysis, there was no significant difference in the odds of cardiovascular death between any testosterone therapy and placebo or among the therapies (eTable11).

Other adverse events: Compared with placebo via meta-analysis, there were no increased odds of any harm outcome associated with the use of testosterone therapy with the exception of withdrawals due to adverse events (eFigures6-9). In the network meta-analysis, there was no difference between any testosterone therapy and placebo or among the therapies for any harm outcome, with the exception of withdrawals due to adverse events (eTables12-15). Use of 1.62% testosterone gel was associated with an increased odds of withdrawal compared with placebo and many of the other testosterone products (eTable15).

Nonrandomized studies

The reporting of harms was generally poor, primarily because of a lack of transparency around the number of patients assigned to each group, the number of events per group, and the type or dose of testosterone product (eTable16). In the largest NRS,[3] among men who had undergone angiography, those who used TRT had a higher risk of an adverse cardiovascular event (HR 1.37, 95%CI 1.21,1.56). Two prospective NRS each reported one myocardial infarction,[27,28] with the occurrence of one in the testosterone group and one in the control group. Stroke was reported by one prospective NRS,[27] with one stroke reported in the testosterone group (n = 26) and one in the control group (n = 23).

Prostate cancer was reported by 5 NRS.[29–33] One cohort study[33] found no increased risk of prostate cancer with testosterone treatment (OR 0.85, 95%CI 0.34,2.16). Rhoden and colleagues[30] reported 1 case of prostate cancer among men using IM testosterone (n = 33) and none among users of 1% gel (n = 25); however, the dose gel and the type of IM testosterone was not reported. The reporting of outcomes and treatment group in the remaining studies was poor: either the group assignment of the men who experienced prostate cancer or the number of men in each treatment group was not reported in each (eTable16).[29,31,32]

DISCUSSION

Despite more than 70 years of clinical use, testosterone therapy remains a controversial area of medicine. Part of the controversy may be a result of different actions of the various testosterone preparations. In an attempt to clarify the benefits and harms of testosterone products, we used traditional pair-wise meta-analysis combined with network meta-analysis, which allows the relative comparison of products that have not been compared in head-to-head trials. Consistent with most previous meta-analyses,[7,10] we found that use of any testosterone product improved quality of life and libido, with no significant effect on erectile function. In contrast with previous reviews, we found no significant effect of testosterone on depression; however, previous meta-analyses have included trials of all durations[8] while we included only

trials with a treatment duration of 12 weeks or longer. A more favourable effect of testosterone on depression in short-term trials (less than 12 weeks) compared with longer trials has been reported.[8]

In the head-to-head comparison of testosterone products via network meta-analysis, we found no significant differences among products in effect on quality of life or erectile function. We found that intramuscular enanthate at 200 mg/2wk was effective at improving symptoms of depression compared to more frequent administration (125 mg/wk) and to Sustanon (100 mg/2 wk), a blend of testosterone esters administered intramuscularly. For libido, testosterone gel (1%, 100 mg/d) was significantly better than testosterone patch (5 mg/d) and oral testosterone undecanoate, and oral testosterone undecanoate at 120 mg/d and intramuscular testosterone undecanoate (1000 mg/12 wk) were both significantly better than oral testosterone undecanoate at 160 mg/d. The finding that a lower dose of oral testosterone undecanoate was more effective than a higher dose was unexpected and requires further investigation.

The FDA and Health Canada have both issued alerts about the potential for cardiovascular-related adverse events among men using testosterone products, based in part on findings from cohort studies,[3,4] the Testosterone in Older Men with Mobility Limitations (TOM) trial,[34] and one meta-analysis.[15] However, Xu and colleagues[15] have been criticized for use of a fixed-effects model, and subsequent reanalysis of their data using a random-effects model found no significant increase in risk of cardiovascular events.[35] Our findings are consistent with previous meta-analyses that have found no increased risk of cardiovascular events compared with placebo.[12–14,16,35,36] Our study extends previous findings by showing no increased risk of any cardiovascular adverse event associated with any individual testosterone product.

Although we had intended to analyze the effects of individual testosterone products among men aged 65 years and older, data were limited because most RCTs included a wide age range. The Testosterone Trials[37,38] were designed to address the lack of data among elderly men. After one year of treatment with 1% testosterone gel, improved sexual activity and desire but not erectile function was reported by men with low sexual function at baseline,[37] with no apparent increase in the risk of adverse cardiovascular

events.[38] Although these findings are encouraging, the trials were not powered to detect adverse events, and the results should not be generalized to different testosterone preparations.

Strengths and limitations

The strengths of this study include a comprehensive search of the published and grey literature without language or date restrictions. In contrast with previous reviews, we included only studies that enrolled men with total testosterone ≤ 12 nmol/L or free testosterone ≤ 225 pmol/L. Although there is no universally agreed on threshold value for low testosterone, a recent guideline recommends testosterone therapy for men with total testosterone lower than 12 nmol/L.[11]

Our study had several limitations. First, the included studies used a variety of assays to determine testosterone levels and a variety of cut-off values for determining "low" testosterone. This has been noted by others.[11,39] The US Centers for Disease Control and Prevention's Hormone Standardization Project[40] will help to resolve this issue. Second, the included RCTs and NRS were generally at unclear or high risk of bias, which may have had an impact on the reliability of subjective data. Third, the duration of treatment may have been too short to see an effect of testosterone therapy for all outcomes. In keeping with the recommendation to reassess symptoms after 3 months of TRT,[21] we included only studies with a treatment duration of 3 months or longer. The median duration of treatment was 6 months, but it is possible that some symptoms may take longer to resolve. Fourth, publication bias could not be assessed for all of the included outcomes because too few trials were included.[18] Based on a visual inspection of the funnel plots, we could not rule out publication bias for any outcome.

Conclusions

To the best of our knowledge, this is the first study to compare the benefits and harms of individual testosterone products among hypogonadal men. Our study builds on previous meta-analyses, comparing the relative effects of individual products, most of which have never been compared in head-to-head

trials. When considered as a group (any testosterone product compared to placebo), testosterone improved quality of life and libido; however, at the individual product level, few had a significant effect on any outcome. We found no increased risk of any major harm with any product; however, this must be viewed in light of the high risk of bias of the included studies, the rare nature of serious harms, and short treatment duration of most studies.

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39. Millar AC, Lau ANC, Tomlinson G, et al. Predicting low testosterone in aging men: a systematic review. *CMAJ* 2016 Jun 20. cmaj.150262

40. Standardizing Hormone Measurements. Atlanta: Centers for Disease Control and Prevention, National Center for Environmental Health Division of Laboratory Sciences; 2014. www.cdc.gov/labstandards/pdf/hs/HoSt_Brochure.pdf. Accessed August 16, 2016.

Figure legends

Figure 1: PRISMA flow diagram showing selection of studies. The number of studies identified in the October 2015 update are noted in parentheses.

Figure 2: Meta-analysis of the effect of testosterone on quality of life. Before (A) and after (B) removal of trials involving men with major comorbidities.

Figure 3: Evidence network for quality of life. The size of each circle (node) is proportional to the number of randomly assigned patients and indicates sample size. The number of randomized controlled trials that contributed to each direct comparison is indicated on each line. IM = intramuscular injection, TC = testosterone cypionate, TE = testosterone enanthate, TU = testosterone undecanoate.

Tables

Table 1: Quality of life – Indirect comparison of testosterone products

	Standardized mean difference (SD)													
	Placebo	**Patch, 5 mg/d**	**Gel 1%, 5 mg/d**	**Gel 1%, 50 mg/d**	**Gel 1%, 75 mg/d**	**Gel 1%, 100 mg/d**	**Gel 2%, 60 mg/d**	**Oral TU, 160 mg/d**	**IM TU, 1000 mg/ 12 wk**	**IM TE, 250 mg/ 3 wk**	**IM TE, 250 mg/ 4 wk**	**IM TC, 200 mg/ 4 wk**	**IM Sustanon, 100 mg/2 wk**	**IM Durateston, 250 mg/4 wk**
Patch, 5 mg/d	-0.80 (0.64)	—												
Gel 1%, 5 mg/d	-0.36 (0.86)	0.44 (1.08)	—											
Gel 1%, 50 mg/d	-0.19 (0.51)	0.61 (0.82)	0.17 (1.00)	—										
Gel 1%, 75 mg/d	0.25 (0.91)	1.06 (1.12)	0.61 (1.25)	0.44 (1.04)	—									
Gel 1%, 100 mg/d	-0.04 (0.86)	0.76 (1.06)	0.32 (1.21)	0.15 (0.99)	-0.29 (1.26)	—								
Gel 2%, 60 mg/d	-0.13 (0.85)	0.68 (1.06)	0.23 (1.20)	0.06 (0.99)	-0.38 (1.25)	-0.09 (1.21)	—							
Oral TU, 160 mg/d	0.26 (0.50)	1.06 (0.81)	0.62 (1.00)	0.45 (0.71)	0.00 (1.04)	0.30 (0.99)	0.38 (0.98)	—						
IM TU, 1000 mg/12 wk	-0.66 (0.39)	0.15 (0.75)	-0.30 (0.94)	-0.47 (0.65)	-0.91 (0.99)	-0.62 (0.94)	-0.53 (0.93)	-0.91 (0.59)	—					
IM TE, 250 mg/3 wk	-0.47 (1.07)	0.33 (0.86)	-0.11 (1.37)	-0.28 (1.19)	-0.73 (1.41)	-0.43 (1.36)	-0.35 (1.36)	-0.73 (1.18)	0.18 (1.14)	—				
IM TE, 250 mg/4 wk	-0.09 (0.88)	0.72 (1.10)	0.27 (1.23)	0.10 (1.03)	-0.34 (1.27)	-0.05 (1.23)	0.04 (1.23)	-0.34 (1.01)	0.57 (0.97)	0.39 (1.39)	—			
IM TC, 200 mg/4 wk	0.10 (1.03)	0.90 (1.21)	0.46 (1.34)	0.29 (1.15)	-0.15 (1.37)	0.14 (1.34)	0.23 (1.33)	-0.16 (1.12)	0.76 (0.95)	0.57 (1.49)	0.19 (1.36)	—		
IM Sustanon, 100 mg/2 wk	0.38 (0.90)	1.19 (1.11)	0.74 (1.25)	0.57 (1.04)	0.13 (1.28)	0.42 (1.25)	0.51 (1.23)	0.13 (1.03)	1.04 (0.99)	0.86 (1.40)	0.47 (1.26)	0.28 (1.37)	—	
IM Durateston 250 mg/4wk	0.10 (1.03)	0.91 (1.21)	0.46 (1.34)	0.29 (1.15)	-0.15 (1.37)	0.14 (1.34)	0.23 (1.33)	-0.15 (1.12)	0.76 (0.95)	0.58 (1.48)	0.19 (1.36)	0.00 (0.96)	-0.28 (1.37)	—

Note: IM = intramuscular injection, TC = testosterone cypionate, TE = testosterone enanthate, TU = testosterone undecanoate.
Standardized mean differences of less than zero indicate that the treatment specified in the row is more effective than the column treatment. To obtain standardized mean differences for comparisons in the opposite direction, negative values should be converted to positive values and vice versa. Bold (green cells) indicate statistical significance.
*Random-effects model.
†Oral TU dose based on testosterone levels at baseline. Patients with total testosterone < 8 nmol/L received 120 mg/d; patients with total testosterone between 8 and 12 nmol/L received 160 mg/d (data not reported by dose).

Figure 1: PRISMA flow diagram showing selection of studies

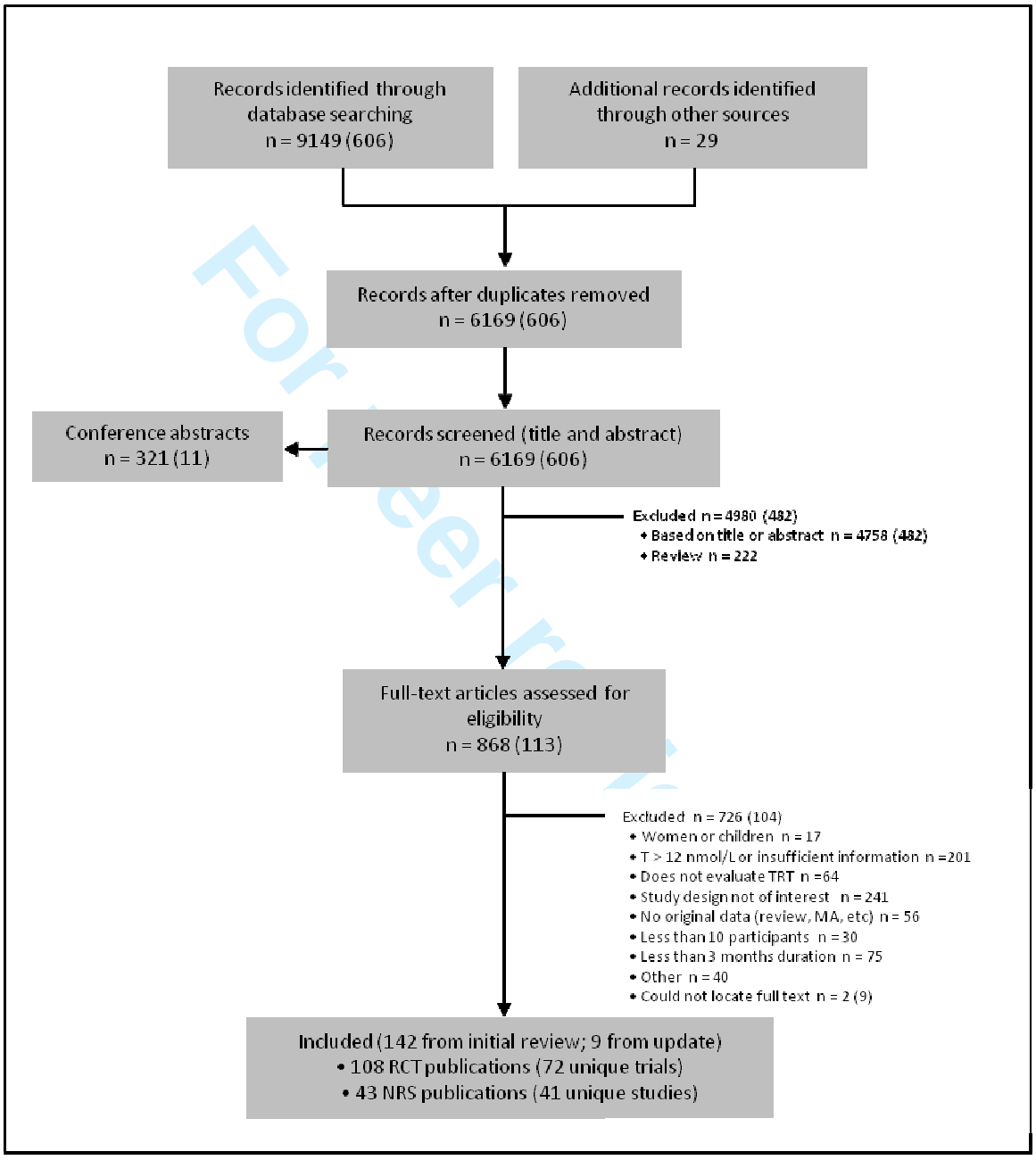
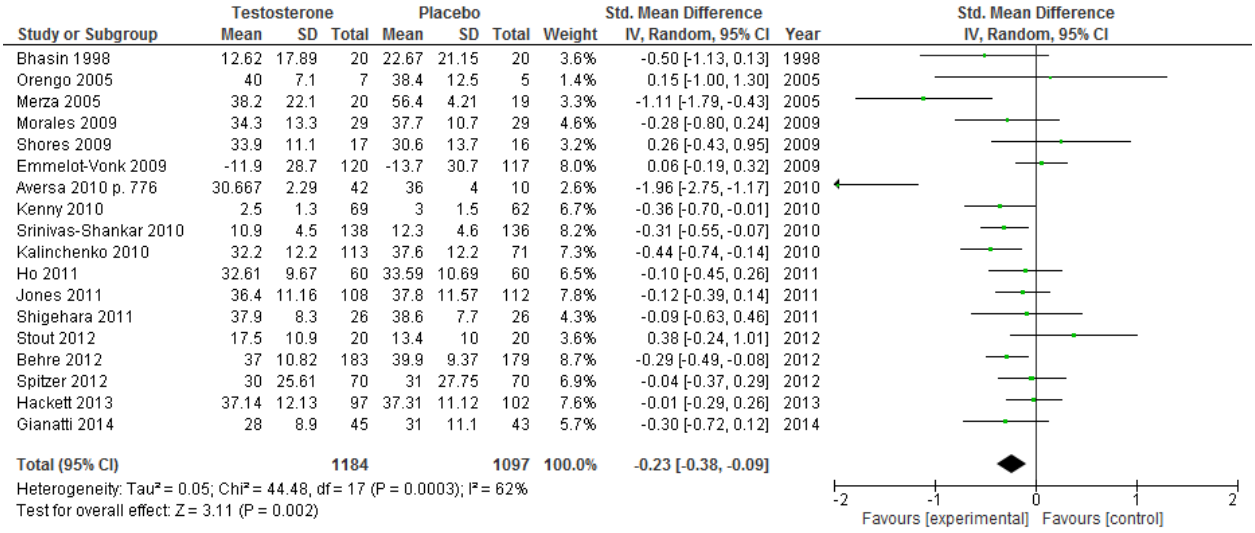


Figure 2: Meta-analysis of the effect of testosterone on quality of life. Before (A) and after (B) removal of trials involving men with major comorbidities

A)



B)

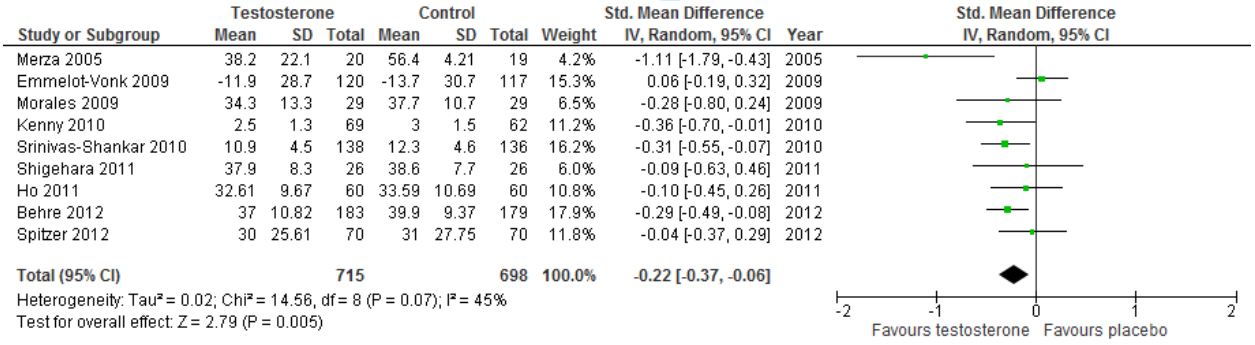
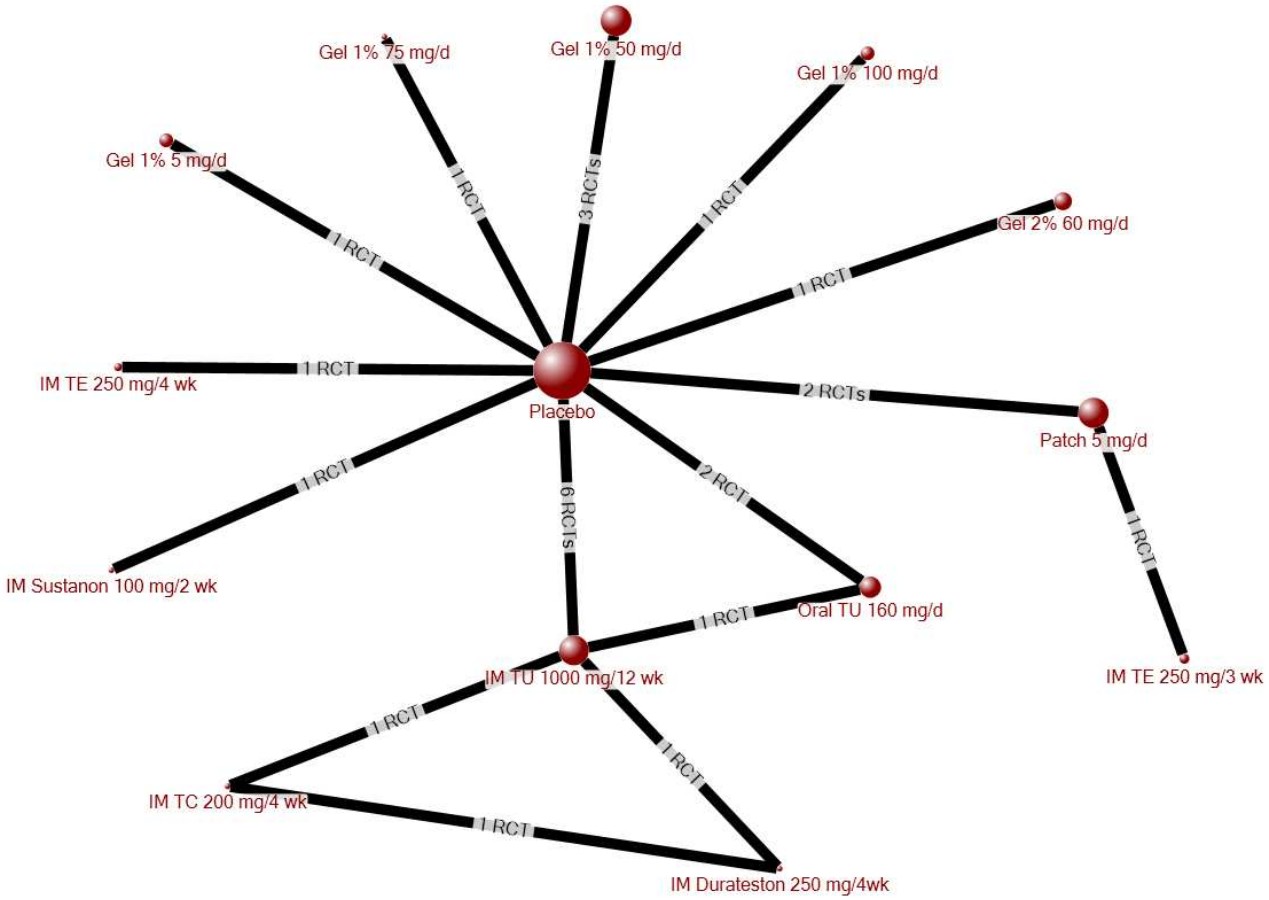


Figure 3: Evidence network for quality of life.



Supplementary Online Content:

Elliott et al. Testosterone replacement therapies in hypogonadal men: a systematic review and network meta-analysis

eAppendix 1: Search strategy

The search was originally executed on June 8, 2014 and updated October 13, 2015. The initial set of numbers in brackets for each line indicates the number of records located in the initial search, with the number located in the updated search indicated in the second set of brackets. The final step in the updated search applied a date limit to identify studies published since the initial search, with retrospective overlap of six months.

Testosterone Replacement Therapy
Primary Studies - Final Strategies
2014 Jun 3

Database: Embase Classic+Embase <1947 to 2014 June 02>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present> Search Strategy:

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1 exp Testosterone/aa, ad, ae, tu (9143) (9790)
2 Testosterone Congeners/ad, ae, tu (391) (397)
3 exp Testosterone/ and Hormone Replacement Therapy/ (4361) (4636)
4 exp Androgens/ and Hormone Replacement Therapy/ (5792) (6109)
5 (testosteron* adj3 (replac* or substitut* or supplement* or therap* or treatment* or buccal or cream$1 or gel or gels or implant* or inject* or oral* or patch* or transdermal*)).tw. (20369) (22080)
6 (androgen* adj (replac* or substitut* or supplement* or therap* or treatment* or cream$1 or gel or gels or implant* or inject* or patch*)).tw. (6312) (6675)
7 (androgen* adj3 (buccal* or oral* or transdermal*)).tw. (632) (690)
8 TRT.tw. (2125) (2597)
9 (testosterone adj (beta cyclopentylpropionate or cyclopentylpropionate or cipionate or cypionate or enanthate or enanthane or ethanate or heptonate or heptylate or oenanthate or undecanoate or undecylate or "17 undecylate")).tw. (2636) (2878)
10 ("8-Isotestosterone" or andriol or "andro 100" or "androgyn LA" or androderm or androfort or androgel or androlin or andronaq or andropatch or androsorb or androstenolone or androtardyl or androtest or androtop or andrusol or axiron).tw. (1095) (1153)
11 ("Bio-T-Gel" or Ciclosterone or "Cristerona T" or "Cristerone T" or CompleoTRT or "CP 601B" or Delatestryl or Depandro or Deposteron or Depostomead or Depo-Testosterone or Depotest or Depovirin or Depoviron or Delatestryl or Duratest or Durathate or Everone or "first-testosterone" or Fortesta or Rortigel or Hexanecarboxylate or Histerone or Homosteron* or Intrinsa or Jenasteron or LibiGel or Livensa or Malerone or Malogen or Malogex or Mertestate).tw. (492) (521)
12 (Nasobol or Nebido or "Neo-Hombreol F" or "Neo-testis" or Neotestis or "NSC 9700" or Opterone or Oreton or "Oreton-F" or Orquisteron).tw. (292) (316)
13 (Pantestone or Perandren or Percutacrine androgenique or Percutacrine androgine or Pertestis or Primotest or Primoteston or Relibra or Restandol or Sterotate or Striant or Sustanon$1 or "Sustason 250" or Synandrol).tw. (674) (695)
14 (Teslen or "Testa-C" or Testamone or Testandrone or Testaqua or Testerone or Testex or Testiculosterone or Testim or Testo Enant or Testobase or Testoderm or Testogel or Testoject-50 or Testolin or Testoluton or Testopel or Testopropon or Testosteroid).tw. (691) (721)
15 (Testostosterone or Testoviron or Testrin or Testro or Testrone or Theramex or Tostrelle or Testryl or Tostrex or Trans-Testosterone).tw. (604) (618)
16 (UNII-3XMK78S47O or Undestor or Virilon or Virormone or Virosterone or Vogelxo).tw. (61) (71)
17 or/1-16 (39453) (42333)
18 exp Animals/ not (exp Animals/ and Humans/) (8702141) (9973287)
19 17 not 18 (25517) (27341)

20 (controlled clinical trial or randomized controlled trial).pt. (457659) (500621)
21 clinical trials as topic.sh. (169995) (179291)
22 (randomi#ed or randomly or RCT$1 or placebo*).tw. (1423548) 1633108
23 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (296647) 325783
24 trial.ti. (292735) 343590
25 or/20-24 (1829141) 2069537
26 19 and 25 (3594) 3936
27 (comment or editorial or interview or letter or news).pt. (2802584) 3104977
28 26 not 27 (3546) 3882
29 (control* adj2 trial*).tw. (323672) 387855
30 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (73609) 84252
31 (nRCT or nRCTs or non-RCT$1).tw. (647) 921
32 (control* adj3 ("before and after" or "before after")).tw. (6046) 6900
33 time series.tw. (33994) 39968
34 (pre- adj3 post-).tw. (110642) 133703
35 (pretest adj3 posttest).tw. (6260) 7263
36 (control* adj2 stud$3).tw. (346641) 393800
37 Control Groups/ (74764) 95125
38 (control$ adj2 group$1).tw. (752277) 862935
39 or/29-38 (1509227) 1742396
40 19 and 39 (2115) 2351
41 40 not 27 (2097) 2327
42 exp Cohort Studies/ (1517558) 1718806
43 cohort$1.tw. (675350) 846152
44 Retrospective Studies/ (837256) 942566
45 (longitudinal or prospective or retrospective).tw. (1721897) 2022768
46 ((followup or follow-up) adj (study or studies)).tw. (89267) 96837
47 Observational study.pt. (2469) 15018
48 (observation$2 adj (study or studies)).tw. (111012) 140783
49 ((population or population-based) adj (study or studies or analys#s)).tw. (26131) 29404
50 ((multidimensional or multi-dimensional) adj (study or studies)).tw. (187) 204
51 Comparative Study.pt. (1676994) 1744032
52 ((comparative or comparison) adj (study or studies)).tw. (185742) 201622
53 or/42-52 (4729450) 5296604
54 19 and 53 (3389) 3800
55 54 not 27 (3352) 3754
56 28 or 41 or 55 (6587) 7288
57 56 use prmz (3219) [ALL MEDLINE RECORDS] 3562
58 28 use prmz (1720) [MEDLINE RCTS] 1902
59 41 use prmz (845) [MEDLINE NON-RCTS] 961
60 55 use prmz (1837) [MEDLINE OBSERV] 2027
61 androgen therapy/ (3539) 4251
62 androgen deficiency/dt (507) 550
63 testosterone undecanoate/ (1591) 1764
64 testosterone cipionate/ (871) 924
65 testosterone enantate/ (2439) 2543
66 (testosteron* adj3 (replac* or substitut* or supplement* or therap* or treatment* or buccal or cream$1 or gel or gels or implant* or inject* or oral* or patch* or transdermal*)).tw. (20369) 22080
67 (androgen* adj (replac* or substitut* or supplement* or therap* or treatment* or cream$1 or gel or gels or implant* or inject* or patch*)).tw. (6312) 6675
68 (androgen* adj3 (buccal* or oral* or transdermal*)).tw. (632) 690
69 TRT.tw. (2125) 2597
70 (testosterone adj (beta cyclopentylpropionate or cyclopentylpropionate or cipionate or cypionate or enanthate or enanthane or ethanate or heptonate or heptylate or oenanthate or undecanoate or undecylate or "17 undecylate")).tw. (2636) 2878
71 ("8-Isotestosterone" or andriol or "andro 100" or "androgyn LA" or androderm or androfort or androgel or androlin or andronaq or andropatch or androsorb or androstenolone or androtardyl or androtest or androtop or andrusol or axiron).tw. (1095) 1153

72 ("Bio-T-Gel" or Ciclosterone or "Cristerona T" or "Cristerone T" or CompleoTRT or "CP 601B" or Delatestryl or Depandro or Deposteron or Depostomead or Depo-Testosterone or Depotest or Depovirin or Depoviron or Delatestryl or Duratest or Durathate or Everone or "first-testosterone" or Fortesta or Rortigel or Hexanecarboxylate or Histerone or Homosteron* or Intrinsa or Jenasteron or LibiGel or Livensa or Malerone or Malogen or Malogex or Mertestate).tw. (492) 521
73 (Nasobol or Nebido or "Neo-Hombreol F" or "Neo-testis" or Neotestis or "NSC 9700" or Opterone or Oreton or "Oreton-F" or Orquisteron).tw. (292) 316
74 (Pantestone or Perandren or Percutacrine androgenique or Percutacrine androgine or Pertestis or Primotest or Primoteston or Relibra or Restandol or Sterotate or Striant or Sustanon$1 or "Sustason 250" or Synandrol).tw. (674) 695
75 (Teslen or "Testa-C" or Testamone or Testandrone or Testaqua or Testerone or Testex or Testiculosterone or Testim or Testo Enant or Testobase or Testoderm or Testogel or Testoject-50 or Testolin or Testoluton or Testopel or Testopropon or Testosteroid).tw. (691) 724
76 (Testostosterone or Testoviron or Testrin or Testro or Testrone or Theramex or Tostrelle or Testryl or Tostrex or Trans-Testosterone).tw. (604) 618
77 (UNII-3XMK78S47O or Undestor or Virilon or Virormone or Virosterone or Vogelxo).tw. (61) 71
78 or/61-77 (33099) 35844
79 randomized controlled trial/ or controlled clinical trial/ (936519) 1028001
80 exp "clinical trial (topic)"/ (104828) 167550
81 (randomi#ed or randomly or RCT$1 or placebo*).tw. (1423548) 1633108
82 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (296647) 325783
83 trial.ti. (292735) 343590
84 or/79-83 (1962147) 2247698
85 78 and 84 (4042) 4646
86 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (37422531) 40432927
87 exp humans/ or exp human experimentation/ or exp human experiment/ (28425359) 31071678
88 86 not 87 (8998814) 9362929
89 85 not 88 (3544) 4094
90 (letter or editorial).pt. (2492646) 2754226
91 89 not 90 (3515) 4053
92 (control* adj2 trial*).tw. (323672) 387855
93 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (73609) 84252
94 (nRCT or nRCTs or non-RCT$1).tw. (647) 921
95 (control* adj3 ("before and after" or "before after")).tw. (6046) 6900
96 time series analysis/ (13996) 16105
97 time series.tw. (33994) 39968
98 pretest posttest control group design/ (202) 246
99 (pre- adj3 post-).tw. (110642) 133703
100 (pretest adj3 posttest).tw. (6260) 7263
101 controlled study/ (4336835) 4757018
102 (control* adj2 stud$3).tw. (346641) 393800
103 control group/ (74764) 95125
104 (control* adj2 group$1).tw. (752277) 862935
105 or/92-104 (5430128) 6026837
106 78 and 105 (7057) 7742
107 106 not 88 (3849) 4336
108 107 not 90 (3833) 4315
109 cohort analysis/ (334727) 409463
110 cohort$1.tw. (675350) 846152
111 retrospective study/ (837256) 991388
112 longitudinal study/ (153245) 179908
113 prospective study/ (618128) 718067
114 (longitudinal or prospective or retrospective).tw. (1721897) 2022768
115 follow up/ (824941) 991095
116 ((followup or follow-up) adj (study or studies)).tw. (89267) 96837
117 observational study/ (58475) 94074
118 (observation$2 adj (study or studies)).tw. (111012) 140783
119 population research/ (68859) 75117
120 ((population or population-based) adj (study or studies or analys#s)).tw. (26131) 29404

Supplemental Online Content: Elliott et al. Testosterone therapy in hypogonadal men: a systematic review and network meta-analysis.

121 ((multidimensional or multi-dimensional) adj (study or studies)).tw. (187) 204
122 exp comparative study/ (2694962) 2848480
123 ((comparative or comparison) adj (study or studies)).tw. (185742) 201622
124 or/109-123 (5973302) 6713482
125 78 and 124 (4650) 5383
126 125 not 88 (3667) 4360
127 126 not 90 (3625) 4304
128 91 or 108 or 127 (7409) 8603
129 128 use emczd (5052) [ALL EMBASE RECORDS] 5966
130 91 use emczd (2221) [EMBASE RCTS] 2611
131 108 use emczd (3091) [EMBASE NON-RCTS] 3471
132 127 use emczd (2341) [EMBASE OBSERV] 2872
133 58 or 130 (3941) [MEDLINE/EMBASE RCTS] 4513
134 remove duplicates from 133 (2771) [UNIQUE RCTS] 3196
135 134 use prmz (1666) [MEDLINE UNIQUE RCTS] 630
136 134 use emczd (1105) [EMBASE UNIQUE RCTS] 2566
137 59 or 131 (3936) [MEDLINE/EMBASE NON-RCTS] 4432
138 137 not 133 (1817) [OVERLAP REMOVED] 2040
139 remove duplicates from 138 (1633) [UNIQUE NON-RCTS] 1818
140 139 use prmz (264) [MEDLINE UNIQUE NON-RCTS] 102
141 139 use emczd (1369) [EMBASE UNIQUE NON-RCTS] 1716
142 60 or 132 (4178) [MEDLINE/EMBASE OBSERV] 4899
143 142 not (133 or 137) (2513) [OVERLAP REMOVED] 2975
144 remove duplicates from 143 (2170) [UNIQUE OBSERV] 2546
145 144 use prmz (1216) [MEDLINE UNIQUE OBSERV STUDIES] 943
146 144 use emczd (954) [EMBASE UNIQUE OBSERV STUDIES] 1603
147 134 or 139 or 144 (6574) [UNIQUE RECORDS – ALL STUDY TYPES] 7560

Limit applied in final line of search update: 2014 to present (Oct. 13, 2015; 6 mo overlap with original search): 606

eAppendix 2: Included studies*

*The list of excluded studies is available from the authors on request.

Note: studies were not evaluated for inclusion on the basis reported outcomes.

1. Agarwal PK, Oefelein MG. Testosterone replacement therapy after primary treatment for prostate cancer. *J Urol.* 2005; 173: 533–6.
2. Agledahl I, Brodin E, Svartberg J, et al. Impact of long-term testosterone treatment on plasma levels of free TFPI and TF-induced thrombin generation ex vivo in elderly men with low testosterone levels. *Thrombo Haemostasis*. 2009; 102: 945.
3. Agledahl I, Hansen JB, Svartberg J. Impact of testosterone treatment on postprandial triglyceride metabolism in elderly men with subnormal testosterone levels. *Scand J Clin Lab Invest* 2008; 68: 641.
4. Amory JK, Watts NB, Easley KA, et al. Exogenous testosterone or testosterone with finasteride increases bone mineral density in older men with low serum testosterone. *J Clin Endocrinol Metab* 2004; 89: 503–10.
5. Andrade ES, Jr., Clapauch R, Buksman S. Short term testosterone replacement therapy improves libido and body composition. *Arq Bras Endocrinol Metabol* 2009;53:996–1004.
6. Arafa M, Zohdy W, Aboulsoud S, et al. Prevalence of late-onset hypogonadism in men with type 2 diabetes mellitus. *Andrologia* 2012; 44: 756.
7. Arver S, Sinha-Hikim I, Beall G, Guerrero M, Shen R, Bhasin S. Serum dihydrotestosterone and testosterone concentrations in human immunodeficiency virus-infected men with and without weight loss. *J Androl* 1999; 20: 611–8.
8. Atkinson RA, Srinivas-Shankar U, Roberts SA, et al. Effects of testosterone on skeletal muscle architecture in intermediate-frail and frail elderly men. *J Gerontol A Biol Sci Med Sci* 2010; 65: 1215.
9. Aversa A, Bruzziches R, Francomano D, et al. Effects of testosterone undecanoate on cardiovascular risk factors and atherosclerosis in middle-aged men with late-onset hypogonadism and metabolic syndrome: results from a 24-month, randomized, double-blind, placebo-controlled study. *J Sex Med* 2010; 7: 3495.
10. Aversa A, Bruzziches R, Francomano D, Spera G, Lenzi A. Efficacy and safety of two different testosterone undecanoate formulations in hypogonadal men with metabolic syndrome. *J Endocrinol Invest* 2010; 33: 776–3.
11. Aversa A,Bruzziches R, Francomano D, et al. Effects of long-acting testosterone undecanoate on bone mineral density in middle-aged men with late-onset hypogonadism and metabolic syndrome: Results from a 36 months controlled study. *Aging Male* 2012; 15: 96.
12. Aydogdu A, Bolu E, Sonmez A, et al. Effects of three different medications on metabolic parameters and testicular volume in patients with hypogonadotropic hypogonadism: 3-year experience. *Clin Endocrinol* 2013; 79: 243–51.
13. Bachman E, Travison TG, Basaria S, et al. Testosterone induces erythrocytosis via increased erythropoietin and suppressed hepcidin: evidence for a new erythropoietin/hemoglobin set point. *J Gerontol A Biol Sci Med Sci* 2014; 69: 725–735.
14. Basaria S, Coviello AD, Travison TG, et al. Adverse events associated with testosterone administration. *N Engl J Med* 2010; 363: 109–22.
15. Basaria S, Davda MN, Travison TG, Ulloor J, Singh R, Bhasin S. Risk factors associated with cardiovascular events during testosterone administration in older men with mobility limitation. *J Gerontol A Biol Sci Med Sci* 2013; 68: 153–160.
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eAppendix 3: Characteristics of the included RCTs and NRS

eTable 1: Characteristics of included RCTs that reported at least 1 outcome of interest

Author, year, page (companion publications)	Population	Duration	Groups (no. randomized)	Age, yr, mean (SD);	Baseline Total T, mean (SD), nmol/L	Industry funding
Borst 2014, p. E433	Hypogonadal men	12 mo	Placebo (16) IM TE, 125 mg/wk (14)	70.8 (9.7) 69.2 (8.0)	8.5 (10.1) 9.2 (11.9)	Mix
Gianatti 2014, p. 2098	Type 2 diabetes, hypogonadal	40 wk	Placebo (43) IM TU, 1000 mg/12 wk (45)	62 (7.4) 62 (8.1)	8.5 (2.8) 8.7 (3.0)	Yes
Hackett 2013 p.1891 (Hackett 2013 p. 1612, Hackett 2014)	T2DM and symptoms of hypogonadism	30 wk	Placebo (102) IM TU, 1000 mg/12 wk (97)	62.0 (9.3) 61.2 (10.5)	8.9 (3.8) 9.2 (3.1)	Yes
Wang 2013, p. 1	Osteoporosis	24 mo	Placebo (62) Oral TU, 20 mg/d (62) Oral TU, 40 mg/d (62)	68.0 (4.8) 68.4 (5.5) 68.1 (5.4)	7.6 (0.7) 7.6 (0.9) 7.4 (0.8)	No
Behre 2012, p. 198	AMS score >36	6 mo	Placebo (179) 1% gel, 50 mg/d (183)	62.1 (6.3) 61.9 (6.6)	10.6 (2.6) 10.4 (2.6)	Yes
Spitzer 2012, p. 681 (Spitzer 2013)	Erectile dysfunction	14 wk	Placebo (70) 1% gel, 100 mg/d (70)	54.6 (8.5) 55.1 (8.3)	8.8 (2.4) 8.6 (2.2)	No
Stout 2012, p. 893	Chronic heart failure	12 wk	Placebo (20) Sustanon,* 100 mg/2 wk (20)	65.9 (8.8) 68.3 (5.3)	11.2 (2.6) 10.4 (2.7)	No
Zhang 2012, p. 3806	Positive score on ADAM questionnaire	6 mo	Vitamin E/C (80) Oral TU, 120 or 160 mg/d (based on T level at baseline)(80)	61.1 (7.1) 59.4 (6.3)	7.7 (0.8) 8.0 (0.7)	No
Ho 2011, p. 260 (Tan 2013, Tong 2012)	At least mild AMS symptoms	42 wk	Placebo (60) IM TU, 1000 mg/12 wk (60)	53.0 (8.2) 53.4 (7.4)	8.9 (2) 9.1 (1.8)	Yes
Jones 2011, p. 828 (Stanworth 2014)	MetS or T2D with at least 2 symptoms of hypogonadism	12 mo	Placebo (112) 2% gel, 60 mg/d (108)	59.9 (9.4) 59.9 (9.1)	9.5 (3.3) 9.2 (2.6)	Yes
Kaufman 2011, p. 2079	Hypogonadal, "otherwise healthy"	6 mo	Placebo (40) 1.62% gel, 40.5 mg/d (234)	55.5 (10.3) 53.6 (9.5)	10.2 (NR) 9.8 (NR)	Yes
Sheffield-Moore 2011, p. E1831	Community-dwelling men	5 mo	Placebo (8) IM TE, 100 mg/wk (8)	65 (3) 73 (8)	11.8 (2.9) 11.9(2.9)	No

Author, year, page (companion publications)	Population	Duration	Groups (no. randomized)	Age, yr, mean (SD);	Baseline Total T, mean (SD), nmol/L	Industry funding
Shigehara 2011, p. 53	Benign prostate hypertrophy	12 mo	No treatment (26) IM TE, 250 mg/4 wk (26)	68.9 (9.1) 72 (6.5)	Free T, pg/ml 6.7 (1.9) 7.0 (1.7)	NR
Aversa 2010, p. 776	MetS or T2DM	6 mo	Placebo (10) Oral TU 160 mg/d (10) IM TU 1000 mg/12 wk (32)	55 (5) 57 (8) 58 (10)	11.1 (NR by group)	NR
Aversa 2010, p. 3495	MetS or T2DM	12 mo	Placebo (10) IM TU, 1000 mg/12wk (40)	57 (8) 58 (10)	9.0 (1.7) 8.33 (2.4)	NR
Basaria 2010, p. 109 (Bachman 2014, Huang 2013, Basaria 2013, Travison 2011)	Limited mobility	6 mo	Placebo (103) 1% gel, 100 mg/d (106)	74 (5) 74 (6)	8.2 (2.3) 8.7 (2.0)	No
Kalinchenko 2010, p. 602 (Giltay 2010)	MetS	30 wk	Placebo (71) IM TU, 1000 mg/12wk (113)	52.8 (9.67) 51.6 (9.76)	7.5 (5.2) 6.7 (3.0)	Yes
Kenny 2010, p. 1134	Low bone mass and frailty	12–24 mo	Placebo (62) 1% gel, 5 mg/d (69)	76.3 (8.0) 77.9 (7.3)	14.5 (6.7) 13.2 (6.2)	Mix
Srinivas-Shankar 2010, p. 639 (O'Connell 2010, Atkinson 2010)	Intermediate-frail and frail	6 mo	Placebo (136) 1% gel, 50 mg/d (138)	73.9 (6.4) 73.7 (5.7)	10.9 (3.1) 11 (3.2)	Yes
Caminiti 2009, p. 919 (Schwartz 2011)	Chronic heart failure	12 wk	Placebo (35) IM TU, 1000 mg/6 wk (35)	69 (66–74) 71 (67–76)	7.3 (7.3) 8.0 (6.2)	No
Chiang 2009, p. 467	Hypogonadal men	3 mo	Placebo (20) 1% gel, 50 mg/d (20)	NR	NR	NR
Emmelot-Vonk, 2009, p. 129 (Emmelot-Vonk 2008, Nakhai-Pour 2007, Buisson 2010)	Moderately low T levels	26 wk	Placebo (117) Oral TU, 160 mg/d (120)	67.4 (4.9) 67.1 (5.0)	10.4 (1.9) 11.0 (1.9)	No
Heufelder 2009, p. 726	MetS and T2DM	52 wk	Placebo (16) 1% gel, 50 mg/d (16)	55.9 (6) 57.3 (5.6)	10.4 (0.8) 10.5 (0.8)	Yes
Hohl 2009, p. 989	High AMS score	12 or 14 wk	IM TU, 1000 mg/6 wk (10) IM TC, 200 mg/4wk (11) Durateston, IM, 250 mg/4wk (11)	59.6 (8.9) 59.6 (7.1) 60.4 (8.8)	9.9 (1.1) 10.1 (1.1) 9.9 (1.5)	No
Mathur 2009, p. 443	Chronic angina pectoris	12 mo	Placebo (7)	67.8 (7.9)	10.1 (2.8)	Yes

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Author, year, page (companion publications)	Population	Duration	Groups (no. randomized)	Age, yr, mean (SD);	Baseline Total T, mean (SD), nmol/L	Industry funding
			IM TU, 1000 mg/12 wk (8)	62.1 (5.2)	9.8 (1.9)	
Morales 2009, p. 104	Sexual dysfunction	4 mo	Placebo (29) Oral TU, 160 mg/d (29)	60.2 (9.6) 59.0 (10.6)	10.0 (5.5) 10.2 (4.9)	Yes
Shores 2009, p. 1009	Dysthymia or minor depression	12 wk	Placebo (16) 1% gel, 75 mg/d (17)	61.7 (7.0) 57.1 (5.7)	9.3 (3.4) 10.1 (3.7)	Mix
Agledahl 2008, p. 641	Subnormal total T	52 wk	Placebo (13) IM TU, 1000 mg/12 wk (14)	69.3 (5.0) 68.9 (5.4)	8.2 (2.4) 8.5 (1.7)	Mix
Basurto 2008, p. 140	Low total T	12 mo	Placebo (23) IM TE, 250 mg/3wk (25)	63.1 (7.7) 63.2 (8.5)	10.8 (1.3) 10.4 (1.1)	No
Raynaud 2008, p. 168	Hypogonadal men	6 mo	Patch, 4.8 mg/d(188) IM TE, 250 mg/3 wk (36)	42.0 (12.7) 40.7 (10.5)	4.6 (3.2 5.1 (3.3)	Yes
Svartberg 2008, p. 378	NR	12 mo	Placebo (19) IM TU, 1000 mg/12 wk (19)	69 (5) 69 (5)	8.2 (2.1) 8.4 (1.7)	Mix
Chiang 2007, p. 411	Hypogonadal men	3 mo	Placebo (20) 1% gel, 50 mg/d (20)	56.1 (14.6) 47.9 (17.0)	9.1 (6.9) 7.4 (5.6)	Yes
Brockenbrough 2006, p. 251	Hemodialysis-dependent end-stage renal disease	6 mo	Placebo (21) 1% gel, 100 mg/d (19)	53.0 (17.2) 58.9 (14.9)	7.0 (3.0) 7.6 (2.2)	Yes
Marks 2006, p. 2351	Symptoms of late-onset hypogonadism	6 mo	Placebo (22) IM TE, 150 mg/2wk (22)	68 (NR) 70 (NR)	8.7 (1.6) 7.7 (1.4)	Mix
Merza 2006, p. 381	Sexual dysfunction	6 mo	Placebo (19) Patch, 5 mg/d (20)	59.7 (10.2) 63.0 (9.0)	7.5 (2.5) 8.4 (3.3)	Yes
Kuhnert 2005, p. 317	Primary, secondary, LOH and symptoms of T deficiency	24 wk	Patch, 5 mg/d (52) 2.5%, gel, 125 mg/d (56) 2.5%, scrotal gel, 25 mg/d (54)	53 (IQR 16) 52.2 (IQR 22.5) 50 (IQR 21)	NR	Yes
Orengo 2005, p. 20	Treatment-resistant depression	12 wk	Placebo (5) 1% gel, 50 mg/d (7)	63 (8.5) (NR by group)	8.9 (1.7) 10.2 (2.3)	No
Amory 2004, p. 503 (Page 2005, Vaughan 2007)	T below the range of normal for young adult men	36 mo	Placebo (24) IM TE 200 mg/2wk (24)	71 (4) 71 (4)	10.1 (2.1) 9.9 (1.6)	No
Cavallini 2004, p. 641	Symptoms of androgen decline	6 mo	Placebo (45) Oral TU, 160 mg/d (40)	63 (NR) 64 (NR)	10.5 (2.1) 9.9 (1.8)	No

Author, year, page (companion publications)	Population	Duration	Groups (no. randomized)	Age, yr, mean (SD);	Baseline Total T, mean (SD), nmol/L	Industry funding
Schubert 2004, p. 5429 (Jockenhovel 2009, Jockenhovel 2009, Minnemann 2008)	Primary or secondary hypogonadism	30 wk	IM TU, 1000 mg/9 wk (20) IM TE, 250 mg/3 wk (20)	41.1 (13.4) 36.3 (12.3)	3.9 (4.4) 2.7 (2.3)	Mix
Shabsigh 2004, p. 658 (Burnett 2013, Wang 2001, Swerdloff 2000)	Erectile dysfunction not responsive to sildenafil	12 wk	Placebo (36) 1% gel, 50 mg/d (39)	59.1 (9.4) 56.8 (10.2)	65% had T < 10.4 (NR by group)	Yes
Boyanov 2003, p. 1	T2DM, obesity, and "symptoms of andropause or erectile dysfunction"	3 mo	No treatment (24) Oral TU, 120 mg/d (24)	All: 57.5 (4.8) (NR by group)	10.76 (11.20) 9.56 (2.33)	NR
McNicholas 2003, p. 69	≥ 1 symptoms of "low T"	90 d	Patch, 5 mg/d (68) 1% gel, 50 mg/d (68) 1% gel, 100 mg/d (72)	57.9 (10.2) 59.0 (9.5) 56.7 (10.3)	7.90 (2.2) 7.95 (2.2) 7.92 (2.4)	Yes
Steidle 2003, p. 2673 (Seftel 2004)	≥ 1 symptoms of "low T"	90 d	Placebo (99) Patch, 5 mg/d (102) 1% gel, 50 mg/d (99) 1% gel, 100 mg/d (106)	56.8 (10.8) 60.5 (9.7) 58.1 (9.7) 56.8 (10.6)	7.9 (2.8) 8.3 (2.4) 8.1 (2.0) 8.1 (2.1)	Yes
Tan 2003, p. 13	Alzheimer's disease	12 mo	Placebo (5) IM TE, 200mg/2wk (5)	68.9 (NR) 72.4 (NR)	NR 3.6 (NR)	No
Ferrando 2002, p. 358 (Ferrando 2003)	"Healthy older men"	6 mo	Placebo (5) IM TE 50–400 mg/wk (7)	67 (6.7) 68 (7.9)	9.8 (4.3) 12.4 (4.4)	No
Kang 2002, p. 862	Coronary artery disease	12 wk	Placebo 17) Oral TU, 160 mg/d (18)	58 (9) 57 (7)	Free T, pg/ml 13.8 (1.8) 9.9 (3.1)	NR
Simon 2001, p. 2149	Healthy adult men	3 mo	Placebo (6) Gel, 125 mg/d (6)	55.4 (3.6) 52.8 (4.2)	9.4 (1.0) 8.3 (0.3)	NR
Bhasin 2000, p. 763	HIV-infected with weight loss	16 wk	Placebo (14) IM TE, 100 mg/wk (17)	41.8 (9.4) 40.8 (4.9)	6.1 (2.9) 7.1 (3.0)	No
Wang 2000, p. 2839	Primary, secondary or late-onset hypogonadism	90 d	Patch, 5 mg/d (76) 1% gel, 50 mg/d (76) 1% gel, 100 mg/d (78)	51.1 (NR) 51.3 (NR) 51.0 (NR)	8.2 (4.8) 8.2 (4.6) 8.6 (4.8)	Mix

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Author, year, page (companion publications)	Population	Duration	Groups (no. randomized)	Age, yr, mean (SD);	Baseline Total T, mean (SD), nmol/L	Industry funding
Clague 1999, p. 261	Community-living	3 mo	Placebo (7) IM TE, 200 mg/2wk (7)	65.3 (1.8) 68.1 (6.6)	11.6 (0.9) 11.3 (1.7)	No
Dobs 1999, p. 3469	Receiving TRT for at least 3 mo	24 wk	Patch, 5 mg/d (33) IM TE, 200 mg/2wk (33)	44.3 (11.1) 44.9 (11.6)	5.8 (2.7) 6.3 (3.3)	Mix
Bhasin 1998, p. 3155 (Arver 1999)	HIV	12 wk	Placebo (21) Patch, 5 mg/d (20)	NR	7.3 (2.9) 9.0 (1.7)	Mix
Grinspoon 1998, p. 18 (Grinspoon 2000)	AIDS wasting syndrome	6 mo	Placebo (26) IM TE, 300 mg/3wk (26)	44 (9) 40 (7)	10.1 (6.4) 11.3 (5.4)	No
Jockenhovel 1997, p. 2510	Primary or secondary androgen deficiency	12 wk	IM TE, 250 mg/3 wk (10) Pellets, 1200 mg (12)	30.0 (7.3) 36.3 (11.1)	1.6 (1.3) 1.9 (1.1)	NR
Jockenhovel 1997, p. 293 (Jockenhovel 1999, Schubert 2001)	Primary or secondary androgen deficiency	210 d	Oral TU, 160 mg/d (13) IM TE, 250 mg/3wk (15) Pellets, 1200 mg (15)	34.5 (14.1) 31.8 (10.1) 35.8 (10.4)	2.9 (1.4) 2.3 (2.3) 2.7 (1.5)	NR
Sih 1997, p. 1661	Community-dwelling healthy men	12 mo	Placebo (15) IM TC, 200 mg/2wk (17)	68 (6) 65 (7)	8.1 (0.7) 10.2 (0.9)	NR

Note: ADAM = androgen deficiency of the aging male, AMS = Aging Males' Symptoms [scale], IM = intramuscular, IQR = interquartile range, LOH = late onset hypogonadism, MetS = metabolic syndrome, NR = not reported, T = testosterone, T2DM = type 2 diabetes mellitus, TC = testosterone cypionate, TE = testosterone enanthate, TRT = testosterone replacement therapy, TU = testosterone undecanoate.
*Blend of testosterone propionate, testosterone phenylpropionate, testosterone isocaproate, and testosterone decanoate.

eTable 2: Characteristics of included non-randomized studies that reported at least one outcome of interest

Study	Population	Duration	Group (no. in group)	Age, yr mean (SD)	Baseline total T, mean (SD), nmol/L*	Industry funding
Retrospective cohort						
Aydogdu 2013, p. 243	IHH	24 wk	Sustanon,† IM 250 mg/3wk (28) 1% gel, 50 mg/d (24)	20.9 (1.4) 21.3 (1.6)	0.9 (0.6) 1.4 (1.3) 1.3 (1.8)	No
Vigen 2013, p. 1829	Men who underwent coronary angiography at a VA medical centre	Mean follow-up: 840 d	TRT, dose NR (1223) No treatment (7486)	60.6 (7.6) 63.8 (9.0 yr)	6.1 (2.2) 7.2 (2.6)	NR
Shores 2012, p. 2050	> 40 yr treated at a VA medical center	20.2 (16.7) mo	TRT, dose NR (398) No treatment (633)	62.1 (10.6)	5.6 (2.2) 6.7 (1.9)	No
Rhoden 2006, p. 201	Hypogonadal men with negative prostate biopsy prior to initiation of TRT	12 mo	IM TRT, dose NR (33) 1% ge, dose NR (25)	58.3	10.3 (5.4) 10.2 (3.1)	No
Guay 2000, p. 132	Men with ED and primary or secondary hypogonadism	2-3 mo	IM TE, 200-300 mg/2-3 wk (25) Patch, 5 mg/d (16)	40–80	Free T: 8.1–9.7 pg/ml	NR
Hajjar 1997, p. 3793	Elderly men	24 mo	IM TE or TC, IM 200 mg/2 wk (45) No treatment (27)	71.8 (SE 1.7) 69.9 (SE 1.9)	10.8 (4.7) 9.6 (3.8)	NR
Prospective cohort						
Francomano 2014, p. 401	Severely obese men (mean BMI 42) with ⍰⍰symptoms of hypogonadism	54 wk	DPE (12) DPE + IM TU, 1000 mg/12 wk (12)	53 (8) 56 (9)	8.2 (1.8) 8.5 (1.8)	NR
Blick 2013, p. 30	HIV/AIDS	12 mo	Androgel 1%, 50 mg/d (92) Testim 1%, 50 mg/d (75)	49.5 (8.1)	13.9 (5.5) 13.7 (7.2)	Yes
Aversa 2012, p. 96	Middle-aged men with LOH and MetS	36 mo	IM TU, 1000 mg/12 wk (40) No treatment (20)	58 (10) 57 (8)	8.3 (2.4)	NR
Dean 2005, p. 87	Aged 21–81 yr	Up to 12 mo	1% gel, 50 mg/d (NR) 1% gel, 100 mg/d (NR)	58.5 (10.0)	8.1 (2.1)	NR
Wang 2004, p.	Aged 19–68 yr	36 mo	1% gel, 50 mg/d (NR)	51.5 (0.9)	14.1 (1.3)	No

Study	Population	Duration	Group (no. in group)	Age, yr mean (SD)	Baseline total T, mean (SD), nmol/L*	Industry funding
2085 (Swerdloff 2003 p.207)			1% gel, 75 mg/d (NR) 1% gel, 100 mg/d (NR)		22.4 (2.7) 25.6 (2.4)	

Note: DPE = diet plus exercise, ED = erectile dysfunction, IHH = idiopathic hypogonadotropic hypogonadism , IM = intramuscular, LOH = late-onset hypogonadism, MetS = metabolic syndrome, NIH = National Institutes of Health, NR = not reported, RCT = randomized controlled trial, SE = standard error, SD = standard deviation, T = testosterone, T2DM = type II diabetes mellitus, TC = testosterone cypionate, TE = testosterone enanthate, TRT = testosterone replacement therapy, VA = Veterans Affairs.

*Unless otherwise stated.

†Blend of estosterone propionate, testosterone phenylpropionate, testosterone isocaproate, and testosterone decanoate.

eTable 3: Risk of bias of included randomized controlled trials that reported at least one outcome of interest

Author, year	Adequate sequence generation	Allocation concealment	Blinding of outcome assessment (objective outcomes)	Blinding of outcome assessment (subjective outcomes)	Incomplete outcome data addressed (efficacy outcomes)	Incomplete outcome data addressed (harm outcomes)
Gianatti 2014	Unclear	Low	Low	Low	Low	Low
Borst 2014	Low	Unclear	Low	High	High	High
Hackett 2013	Unclear	Low	Low	Low	Low	Low
Wang 2013	Unclear	Unclear	Low	NA	Low	High
Behre 2012	Low	Low	Low	Low	Low	High
Spitzer 2012	Unclear	Low	Low	Low	Low	Low
Stout 2012	Unclear	Unclear	NA	Low	High	High
Zhang 2012	Unclear	Low	Low	High	Low	Low
Ho 2011	Unclear	Low	Low	Low	Low	Low
Jones 2011	Unclear	Unclear	Low	Low	High	High
Kaufman 2011	Unclear	Low	Low	Low	High	Low
Sheffield-Moore 2011	Unclear	Low	Low	NA	Low	High
Shigehara 2011	Unclear	Unclear	Low	High	Low	Low
Aversa 2010, p. 776	Unclear	Unclear	Low	Low	Unclear	Unclear
Aversa 2010, p. 3495	Unclear	Unclear	Low	Low	Low	Low
Basaria 2010	Low	Low	Low	Low	Low	Unclear
Kalinchenko 2010	Unclear	Low	Low	Low	Low	Low
Kenny 2010	Unclear	Low	Low	Low	High	Unclear
Srinivas-Shankar 2010	Low	Low	Low	Low	Low	Unclear
Caminiti 2009	Unclear	Low	Low	Low	Low	Low
Chiang 2009	Unclear	Unclear	Low	Low	High	High
Emmelot-Vonk 2009	Low	Low	Low	Low	Low	Low
Heufelder 2009	Low	Unclear	Low	High	Low	Low
Hohl 2009	High	High	Low	High	Low	Low
Mathur 2009	Low	Unclear	Low	Low	Low	High
Morales 2009	Low	Low	Low	Low	Low	Low
Shores 2009	Low	Low	Low	Low	High	Unclear
Agledahl 2008	Unclear	Unclear	Low	NA	Low	Low

Basurto 2008	Low	Low	Low	Low	Low	Unclear
Raynaud 2008	Unclear	Unclear	Low	High	High	High
Svartberg 2008	Unclear	Unclear	Low	Low	Low	Unclear
Chiang 2007	Unclear	Unclear	Low	Unclear	High	Low
Brockenbrough 2006	Unclear	Low	Low	Unclear	High	Low
Marks 2006	Unclear	Unclear	Low	Low	Low	Low
Merza 2005	Unclear	Unclear	Low	Unclear	Low	Low
Kuhnert 2005	Unclear	Low	Low	High	High	High
Orengo 2005	Low	Unclear	Low	Unclear	High	High
Amory 2004	Low	Low	Low	Low	Unclear	Unclear
Cavallini 2004	Unclear	Unclear	Low	Unclear	Unclear	High
Schubert 2004	Low	Unclear	Low	High	Unclear	Low
Shabsigh 2004	Low	Unclear	Low	Low	Low	Unclear
Boyanov 2003	Unclear	Unclear	Low	High	Low	Low
McNicholas 2003	Unclear	Unclear	Low	High	High	High
Steidle 2003	Unclear	Unclear	Low	High	High	High
Tan 2003	Unclear	Unclear	Unclear	High	Low	Low
Ferrando 2002	Unclear	Unclear	Low	NA	Low	Low
Kang 2002	Unclear	Unclear	Low	NA	Low	Low
Simon 2001	Unclear	Unclear	Low	Low	NA	Low
Bhasin 2000	Low	Unclear	Low	Unclear	Low	Unclear
Wang 2000	Unclear	Unclear	Low	High	High	High
Clague 1999	Unclear	Unclear	Low	NA	Low	Low
Dobs 1999	Unclear	Low	Low	High	High	Unclear
Bhasin 1998	Unclear	Unclear	Low	Unclear	High	Unclear
Grinspoon 1998	Low	Low	Low	Low	High	Unclear
Jockenhovel 1997, p. 2510	Unclear	Unclear	Low	NA	Unclear	Unclear
Jockenhovel 1997, p. 293	Unclear	Unclear	Low	NA	Low	Unclear
Sih 1997	Low	Unclear	Low	Unclear	High	Unclear

Note: Risk of bias was not assessed for the studies that reported no outcomes of interest or that did not provide usable data (e.g., cross-over studies without first period data reported separately).

eTable 4: SIGN50 assessment of included non-randomized studies that reported at least one outcome of interest

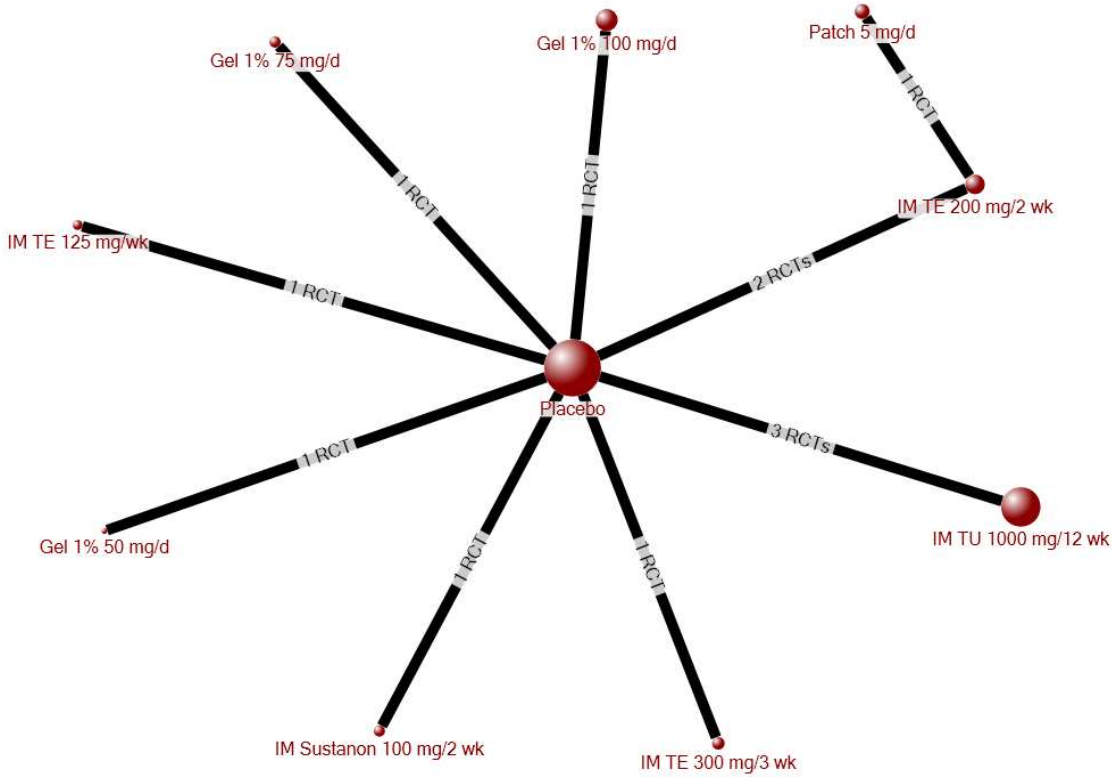
Study*	Overall assessment†	Comments
Francomano 2014	Unacceptable (–)	Prospective cohort. Obese men with low testosterone. Baseline characteristics were well matched on reported characteristics, but control group had contraindications to TRT. 33% dropout in treatment group, zero in control group; no comparison between those who dropped out or remained in study.
Aydogdu 2013	Acceptable (+)	Retrospective cohort. Men with IHH. SAE not defined as an outcome but reported that no SAEs were detected for any treatment group.
Blick 2013	Acceptable (+)	Prospective cohort. Groups were generally well matched on baseline characteristics with no statistically significant differences (except for study site). Patients in the 2 treatment groups were not followed for an equal length of time (Androgel: mean 6.1 yr; Testim: mean 1.9 yr). Skin reactions assessed but not reported. Outcome assessment was not blinded to exposure status.
Vigen 2013	Acceptable (+)	Retrospective cohort. All-cause mortality assessed via the Veterans Affairs vital status file. Myocardial infarction and ischemic stroke assessed via ICD-9 codes from Veterans Affairs inpatient treatment files. Conclusions based on a composite outcome. Sufficient data not reported to allow analysis of stroke or MI separately at each time point. Outcome assessment not blinded to exposure status.
Aversa 2012	Unacceptable (–)	Prospective cohort. Men with multiple sclerosis and late onset hypogonadism. Baseline characteristics were well matched but the control group comprised of men who had refused or had contraindications to testosterone. Adherence to treatment over 3 years was 50% in TU group. Those discontinuing TU but remaining in study for follow up were not included in efficacy analysis.
Shores 2012	Acceptable (+)	Retrospective cohort. Hazard ratio for mortality takes person-years of observation into account. Adjusted HR and CIs provided (adjusted for age, site, hospitalization in the past year, diabetes, coronary artery disease). Outcome assessment not blinded to exposure status. Exposure determined via Veterans Affairs pharmacy records and outcomes ascertained from 2 mortality databases.
Rhoden 2006	Acceptable (+)	Retrospective cohort. Patients had to have negative prostate biopsy before initiation of TRT, thus excluding any men with pre-existing large volume disease. Type and dose of IM testosterone not reported. Dose of gel not reported (data NR by type). Outcome assessment not blinded to exposure status.
Dean 2005	Unacceptable (–)	Prospective cohort. Poor reporting of the number of patients in each group and which group the safety events occurred in. Number of and reasons for withdrawals not reported. Safety data reported overall but not by treatment group. Outcome assessment not blinded to exposure status.
Wang 2004	Unacceptable (–)	Prospective cohort (open-label extension of an RCT). The number of men assigned to each group NR. Safety data poorly reported: 3 cases of prostate cancer reported but number of people in each group not reported. Outcome assessment not blinded to exposure status.
Guay 2000	Unacceptable (–)	Retrospective cohort. Safety data not reported by treatment group. Outcome

Study*	Overall assessment†	Comments
		assessment not blinded to exposure status.
Hajjar 1997	Unacceptable (–)	Retrospective cohort. Data not clearly provided. Safety outcomes were reported based on a subset of people assigned to each group, and it is not clear why the other patients were omitted. Outcome assessment not blinded to exposure status.

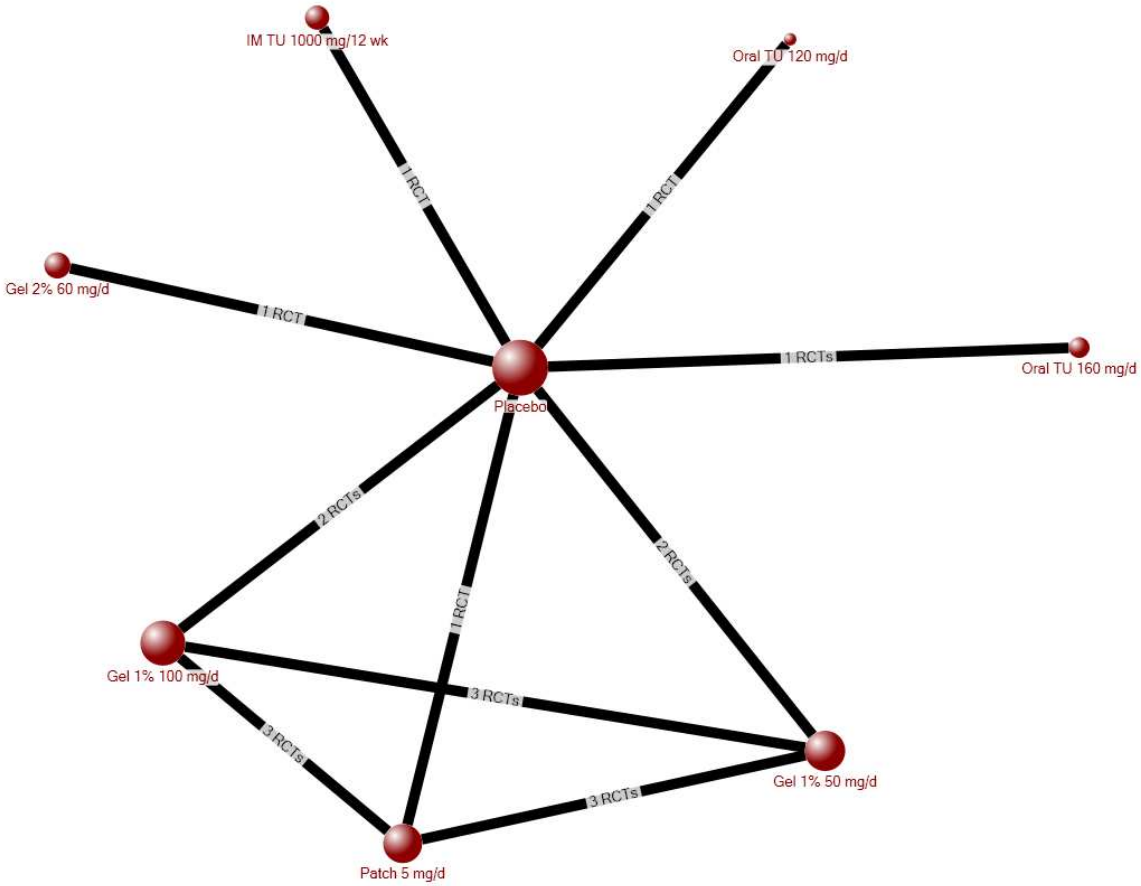
Note: CI = confidence interval, ICD = International Classification of Diseases, Ninth Revision, IHH = idiopathic hypogonadotropic hypogonadism, HR = hazard ratio, MI = myocardial infarction, NR = not reported, RCT = randomized controlled trial, SAE = serious adverse events, TRT = testosterone replacement therapy, TU = testosterone undecanoate.
*Non-randomized studies that reported at least 1 outcome of interest.
†Assessed by use of SIGN50 for cohort studies.

eAppendix 4: Evidence networks

eFigure 1A) Depression

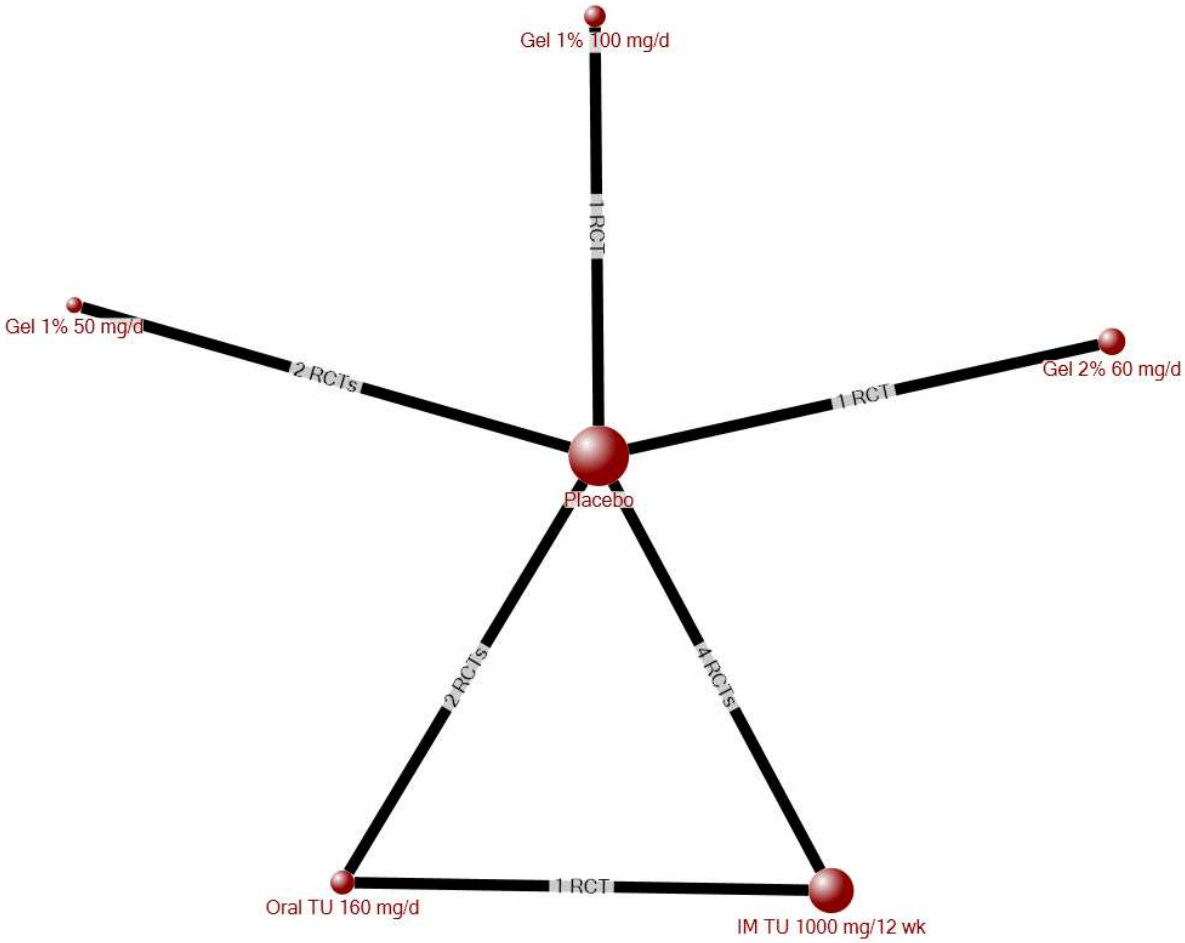


B) Libido



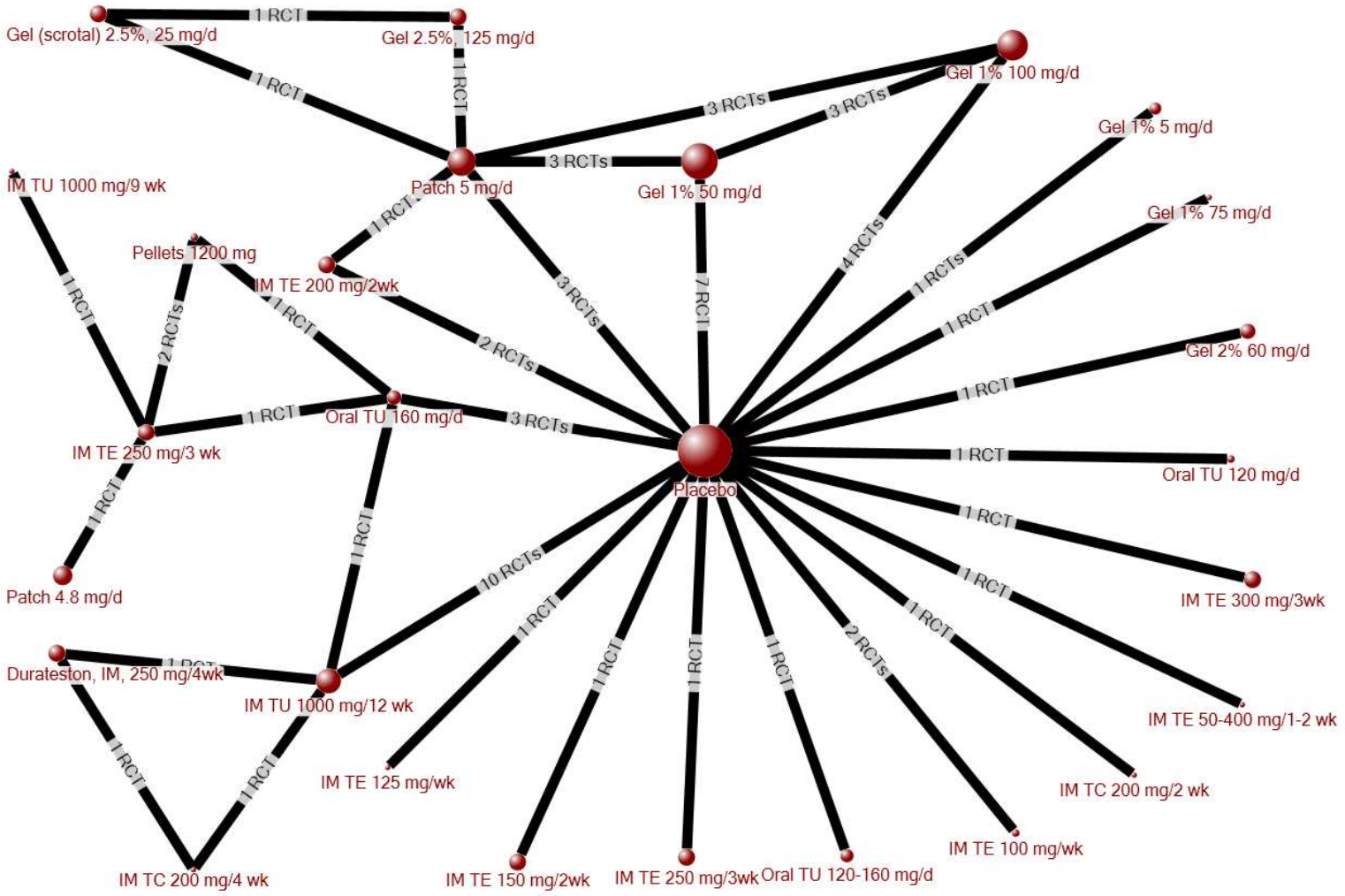
Supplemental Online Content: Elliott et al. Testosterone therapy in hypogonadal men: a systematic review and network meta-analysis.

C) Erectile function



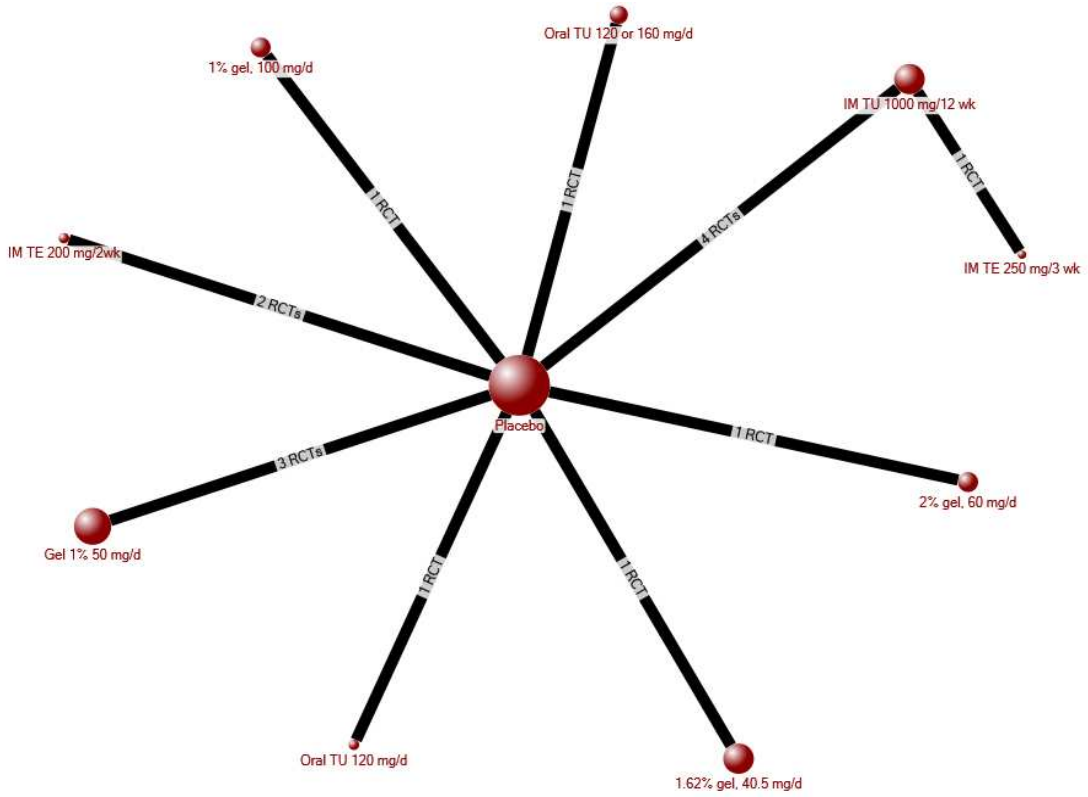
Supplemental Online Content: Elliott et al. Testosterone therapy in hypogonadal men: a systematic review and network meta-analysis.

D) Total serum testosterone, end of study



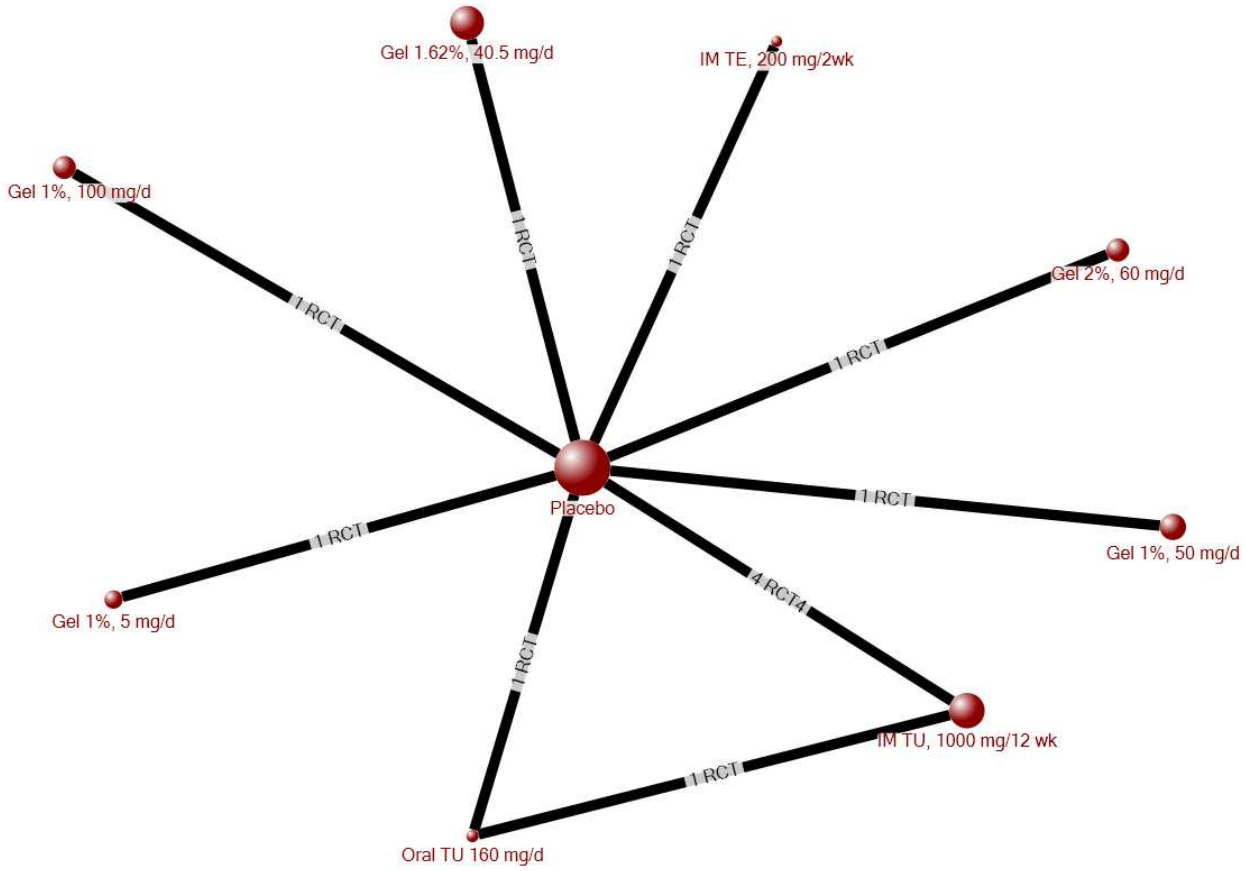
Supplemental Online Content: Elliott et al. Testosterone therapy in hypogonadal men: a systematic review and network meta-analysis.

E) Cardiovascular death



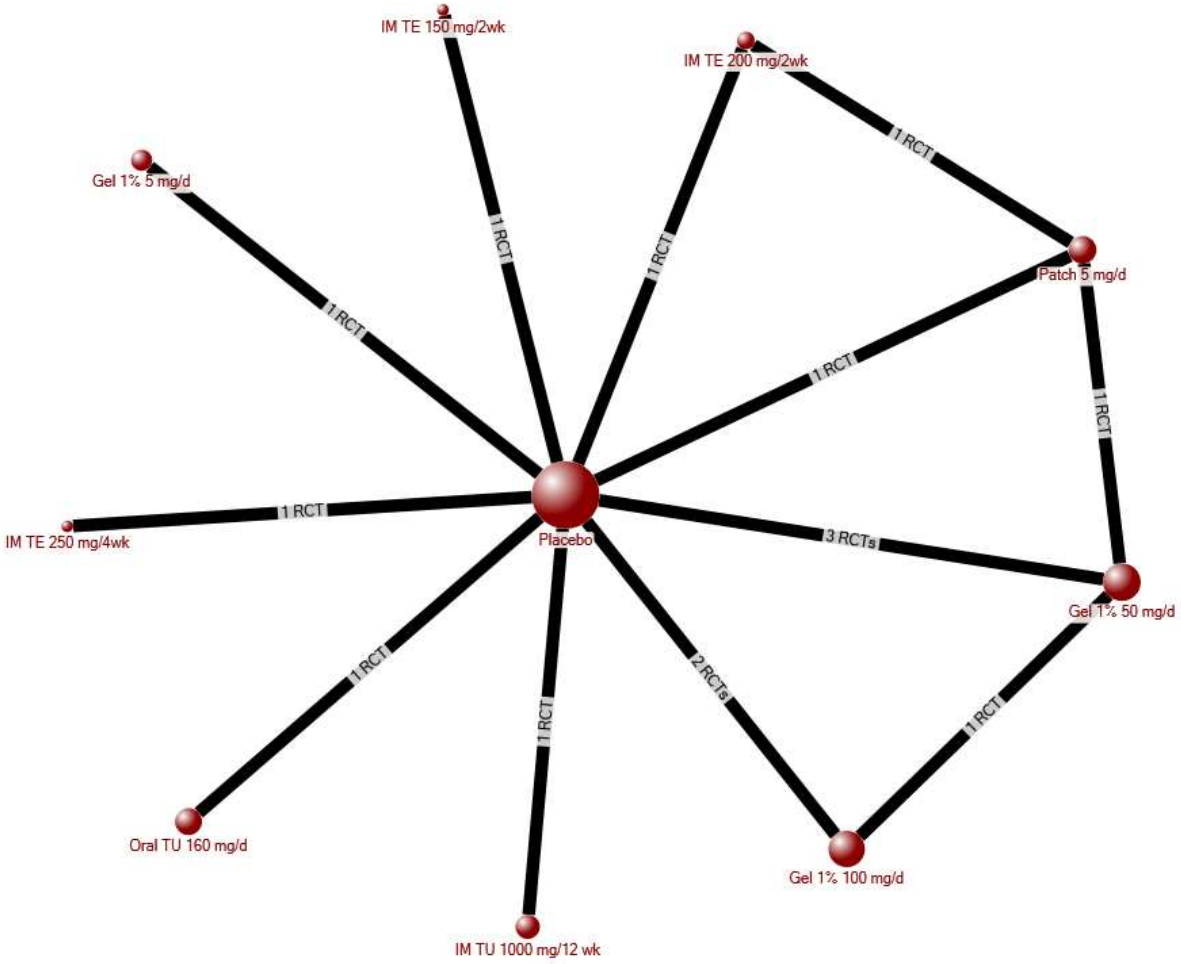
Supplemental Online Content: Elliott et al. Testosterone therapy in hypogonadal men: a systematic review and network meta-analysis.

F) Myocardial infarction



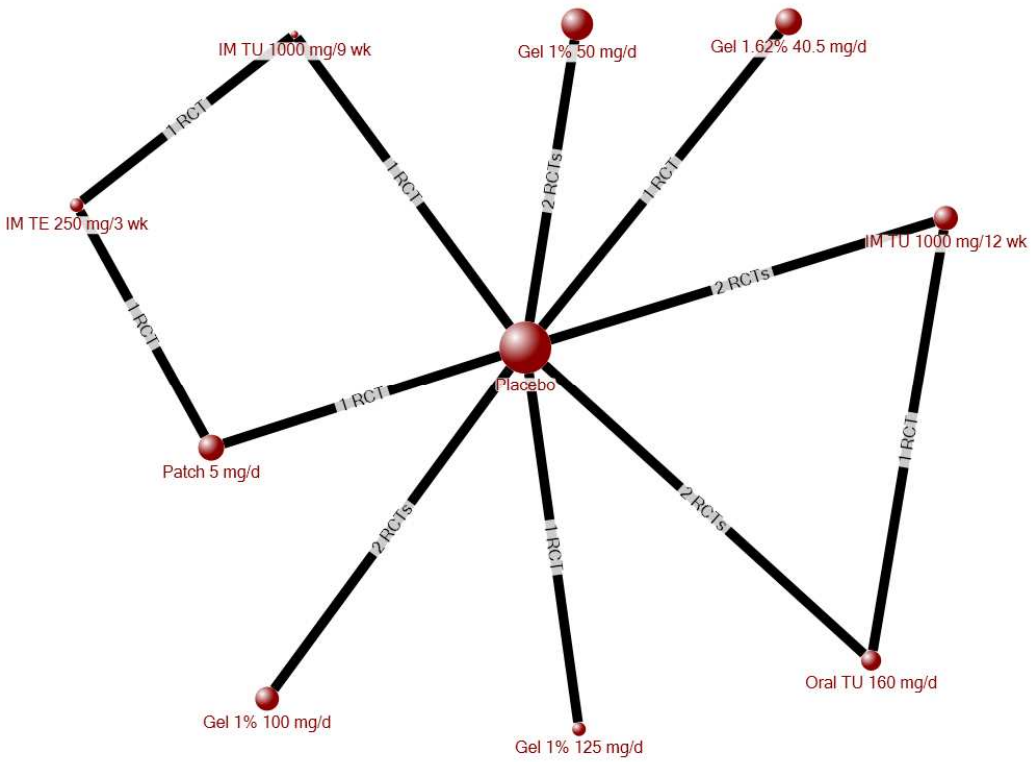
Supplemental Online Content: Elliott et al. Testosterone therapy in hypogonadal men: a systematic review and network meta-analysis.

G) Prostate cancer



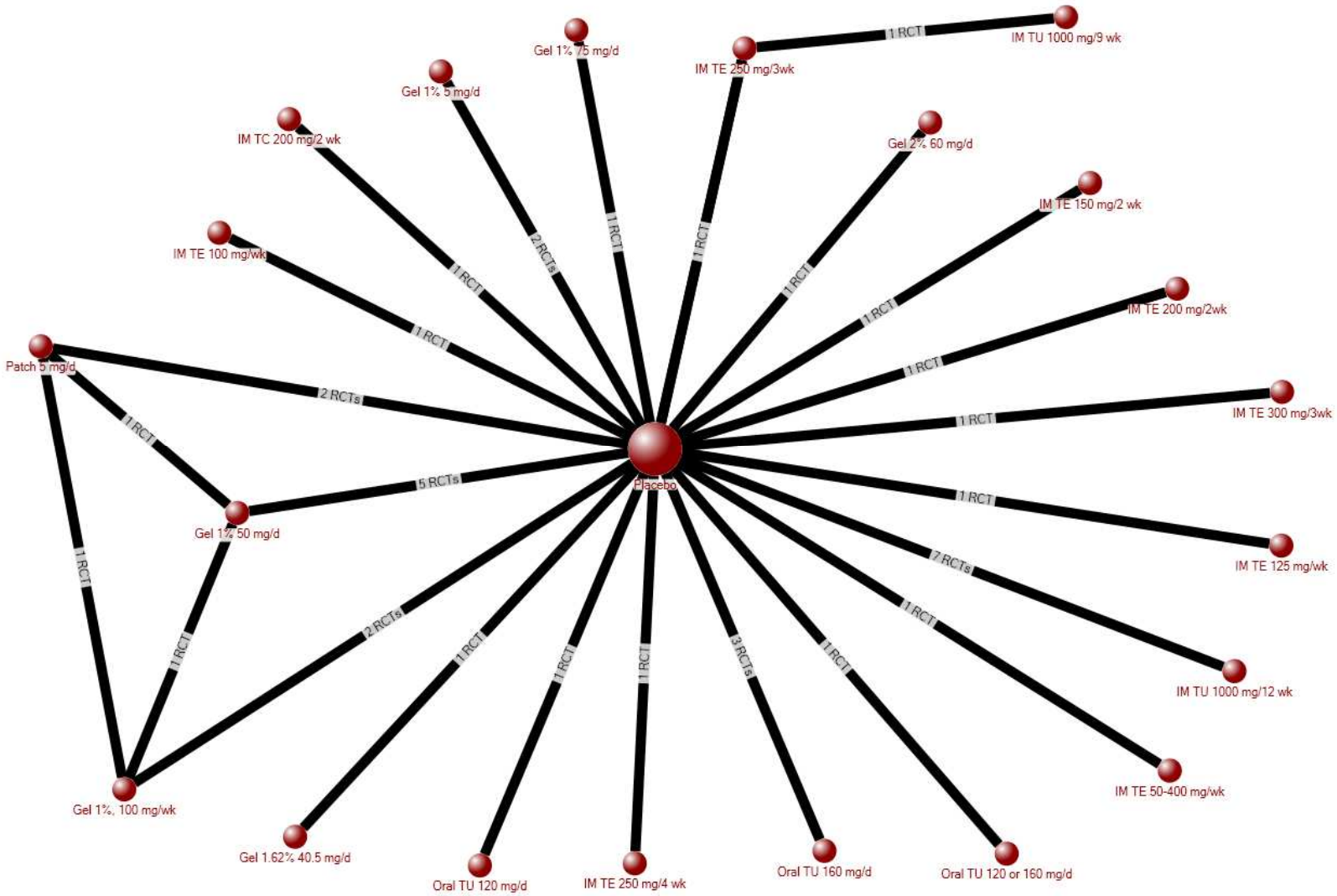
Supplemental Online Content: Elliott et al. Testosterone therapy in hypogonadal men: a systematic review and network meta-analysis.

H) Serious adverse events



Supplemental Online Content: Elliott et al. Testosterone therapy in hypogonadal men: a systematic review and network meta-analysis.

I) Withdrawals due to adverse events



Supplemental Online Content: Elliott et al. Testosterone therapy in hypogonadal men: a systematic review and network meta-analysis.

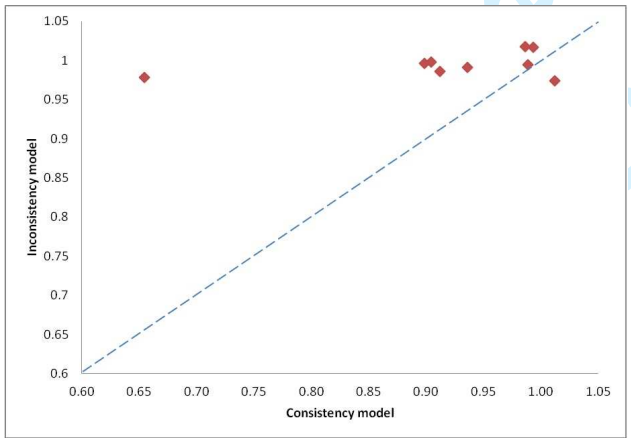
eAppendix 5: Evaluation of network consistency

We evaluated the consistency of networks with closed loops. To be classified as a "closed loop," at least 2 nodes had to be connected by more than one trial (e.g., not connected solely by a multi-arm trial).

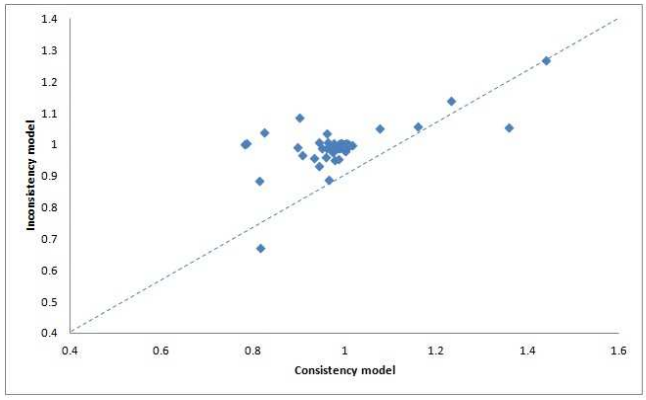
To evaluate the consistency of networks with closed loops, two analyses were performed. One was conducted using the standard consistency model, which assumes that the data in the network are consistent. A second analysis was performed using an inconsistency model, which assumes that the data in the network are not consistent. The posterior mean deviance of the individual data points derived from the inconsistency model was plotted against the posterior mean deviance derived from the consistency model. If inconsistency is present, data points will lie under the diagonal line, indicating deviation from the consistency model. Data points above the diagonal line indicate deviation from the inconsistency model and are not indicative of inconsistency.

Model fit was also evaluated by considering the residual deviance and deviance information criterion (DIC) of the inconsistency and consistency models, with the model that has the lower residual deviance and DIC representing the better fit for the data. For each network, the consistency model had a lower residual deviance and DIC for each outcome, representing better model fit.

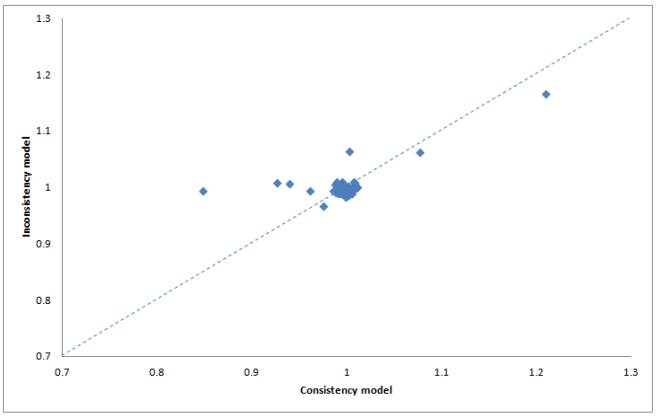
LIBIDO: BASE CASE (ALL STUDIES)



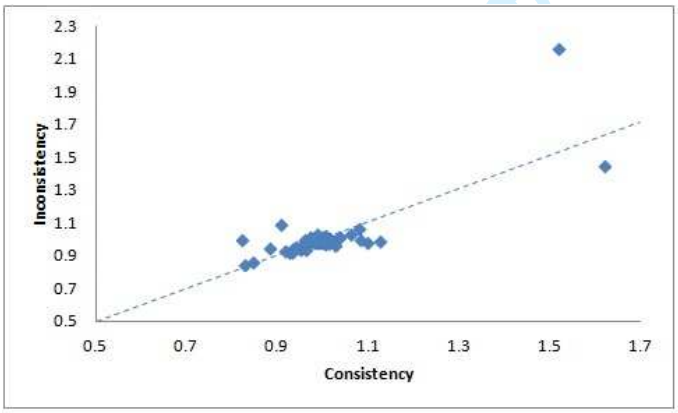
TOTAL TESTOSTERONE LEVEL, 3 MO



TOTAL TESTOSTERONE LEVEL, 6 MO



TOTAL TESTOSTERONE LEVEL, END OF STUDY



eAppendix 6: Pair-wise meta-analyses and network meta-analyses

Note: The indirect comparison staircase diagrams (Bayesian network meta-analyses) are read by comparing the row treatment against the column treatment. Green indicates a significantly better outcome and red indicates a statistically worse outcome for the row treatment relative to the column treatment. Results are reported for random-effects models.

Summary of network characteristics

Outcome	No. of trials	No. of treatments*	No. of comparisons†	No. of participants	Treatment duration
Benefits					
Quality of life	20	13	24	2698	12 wk to 1 yr
Depression	11	9	11	842	12 wk to 36 mo‡
Libido	9	7	18	1546	12 wk to 1 yr
Erectile function	10	5	12	1053	12 wk to 1 yr
Activities of daily living	0	—	—	—	—
Harms					
Cardiovascular death	15	9	15	2089	12 wk to 36 mo‡
Myocardial infarction	11	8	13	1638	6 to 36 mo§
Prostate cancer	11	9	16	2024	24 wk to 36 mo§
Serious AEs	14	9	16	2260	12 to 42 wk
Withdrawals due to AEs	41	21	43	3908	12 wk to 36 mo§
Meta-analysis¶	**No. of trials**	**Odds ratio (95% CI)**	**I^2**	**No. of participants**	**Treatment duration**
Stroke	4	0.50 (0.05, 4.85)	25%	329	5 to 36 mo‡
Diabetes	0	—	—	—	—
Heart disease	3	0.89 (0.24 to 3.26)	0%	251	40 wk to 12 mo
Erythrocytosis	3	2.44 (0.26, 22.53)	0%	104	6 to 12 mo

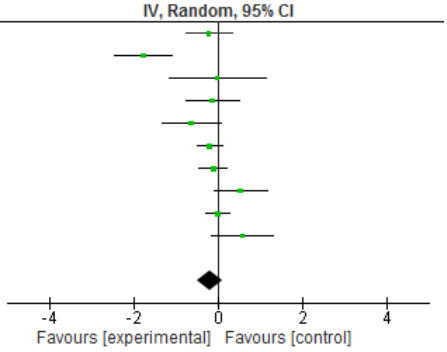
Note: AE = adverse event, IM = intramuscular, TE = testosterone enanthate, TU = testosterone undecanoate, T = testosterone, TRT = testosterone replacement therapy
***In addition to placebo**
†Direct comparisons based on the number of 2-, 3-, and 4-arm trials.
‡One study with a treatment duration longer than 12 mo.
§Two trials with a treatment duration longer than 12 mo.
¶Insufficient data for stroke, diabetes, heart disease, and erythrocytosis were available for analysis by network meta-analysis.

eFigure2: Individual trial results, depression

A) All trials

Study or Subgroup	Testosterone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Grinspoon 1998	9.2	7.1	26	10.8	8.2	26	10.4%	-0.21 [-0.75, 0.34]	1998
Amory 2004	3.1	0.6	24	4.8	1.2	24	8.9%	-1.76 [-2.44, -1.09]	2004
Orengo 2005	9.4	4.4	7	9.4	9.7	5	4.9%	0.00 [-1.15, 1.15]	2005
Svartberg 2008	3.8	4.8	19	4.3	2.8	19	9.3%	-0.12 [-0.76, 0.51]	2008
Shores 2009	8.4	5	17	11.4	4.4	16	8.6%	-0.62 [-1.32, 0.08]	2009
Kalinchenko 2010	6.1	5.75	113	7.2	6.58	71	13.5%	-0.18 [-0.48, 0.12]	2010
Spitzer 2012	15	19.2	70	17	19.2	70	13.1%	-0.10 [-0.44, 0.23]	2012
Stout 2012	6.6	3.8	20	4.6	3.4	20	9.4%	0.54 [-0.09, 1.18]	2012
Hackett 2013	6.85	3.91	97	6.85	4.1	102	13.7%	0.00 [-0.28, 0.28]	2013
Borst 2014	3.33	3.39	14	1.83	1.27	16	8.2%	0.59 [-0.15, 1.32]	2014
Total (95% CI)			**407**			**369**	**100.0%**	**-0.18 [-0.49, 0.13]**	

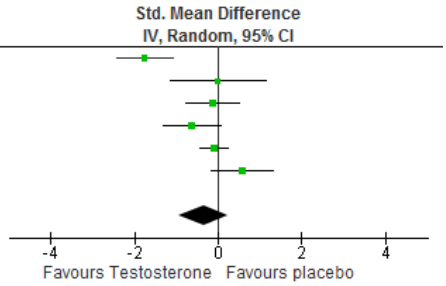
Heterogeneity: Tau² = 0.16; Chi² = 33.45, df = 9 (P = 0.0001); I² = 73%
Test for overall effect: Z = 1.16 (P = 0.25)



B) Trials involving men without major comorbidities

Study or Subgroup	Testosterone Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Amory 2004	3.1	0.6	24	4.8	1.2	24	17.0%	-1.76 [-2.44, -1.09]	2004
Orengo 2005	9.4	4.4	7	9.4	9.7	5	12.1%	0.00 [-1.15, 1.15]	2005
Svartberg 2008	3.8	4.8	19	4.3	2.8	19	17.4%	-0.12 [-0.76, 0.51]	2008
Shores 2009	8.4	5	17	11.4	4.4	16	16.7%	-0.62 [-1.32, 0.08]	2009
Spitzer 2012	15	19.2	70	17	19.2	70	20.4%	-0.10 [-0.44, 0.23]	2012
Borst 2014	3.3	3.39	14	1.83	1.27	16	16.4%	0.57 [-0.16, 1.31]	2014
Total (95% CI)			**151**			**150**	**100.0%**	**-0.35 [-0.95, 0.25]**	

Heterogeneity: Tau² = 0.43; Chi² = 26.18, df = 5 (P < 0.0001); I² = 81%
Test for overall effect: Z = 1.16 (P = 0.25)



eTable 5: Depression at end of treatment – Bayesian network meta-analysis

	Standardized mean difference (standard deviation)									
	Placebo	**Patch, 5 mg/d**	**Gel 1%, 50 mg/d**	**Gel 1%, 75 mg/d**	**Gel 1%, 100 mg/d**	**IM TU, 1000 mg/12 wk**	**IM TE, 125 mg/ wk**	**IM TE, 200 mg/ 3 wk**	**IM TE, 300 mg/ 3 wk**	**IM Sustanon, 100 mg/ 2 wk**
Patch, 5 mg/d	-1.98 (1.22)	—								
Gel 1%, 50 mg/d	-0.02 (1.00)	1.97 (1.58)	—							
Gel 1%, 75 mg/d	-0.62 (0.89)	1.36 (1.52)	-0.60 (1.33)	—						
Gel 1%, 100 mg/d	-0.10 (0.82)	1.88 (1.49)	-0.09 (1.28)	0.52 (1.20)	—					
IM TU, 1000 mg/12 wk	-0.10 (0.49)	1.89 (1.31)	-0.08 (1.10)	0.52 (1.01)	0.01 (0.96)	—				
IM TE 125 mg/wk	0.60 (0.89)	2.58 (1.51)	0.61 (1.34)	1.22 (1.27)	0.70 (1.21)	0.69 (1.00)	—			
IM TE, 200 mg/2 wk	-1.78 (0.88)	0.20 (0.86)	-1.76 (1.34)	-1.16 (1.26)	-1.68 (1.20)	-1.68 (1.01)	-2.38 (1.25)	—		
IM TE, 300 mg/3 wk	-0.21 (0.87)	1.78 (1.51)	-0.19 (1.33)	0.41 (1.25)	-0.10 (1.19)	-0.11 (1.00)	-0.80 (1.25)	1.57 (1.24)	—	
IM Sustanon, 100 mg/2 wk†	0.55 (0.87)	2.53 (1.50)	0.56 (1.32)	1.17 (1.26)	0.65 (1.20)	0.64 (0.99)	-0.05 (1.24)	2.33 (1.24)	0.75 (1.24)	—

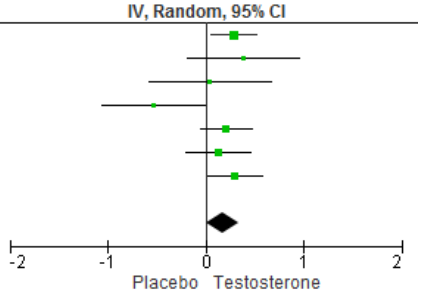
Note: IM = intramuscular, TE = testosterone enanthate, TU = testosterone undecanoate.
***Oral TU dose was based on testosterone levels at baseline. Patients with total testosterone < 8 nmol/L received 120 mg/d; patients with testosterone between 8 and 12 nmol/L received 160 mg/d (data not reported by dose)**
†Blend of testosterone propionate, testosterone phenylpropionate, testosterone isocaproate, and testosterone decanoate.
Note: a negative SMD indicates improvement in depression. Significant changes are indicated by use of bold and colour (green indicates that the row treatment treatement is significantly better than the column treatment, which red indicates that the row treatment is signigicantly worse than the column treatment).

eFigure3: Individual trial results, libido

A) All trials

Study or Subgroup	Testosterone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Steidle 2003	3	1.4	307	2.6	1.4	99	23.7%	0.29 [0.06, 0.51]	2003
Boyanov 2003	2.1	0.6	24	1.7	1.3	24	7.0%	0.39 [-0.18, 0.96]	2003
Chiang 2009	6.4	1.6	20	6.3	2.4	20	6.1%	0.05 [-0.57, 0.67]	2009
Morales 2009	5	2	29	6.1	2.1	29	8.0%	-0.53 [-1.05, -0.00]	2009
Jones 2011	6.3	2.2	108	5.8	2.6	112	20.4%	0.21 [-0.06, 0.47]	2011
Spitzer 2012	10.5	4.3	70	10	3.2	70	15.7%	0.13 [-0.20, 0.46]	2012
Hackett 2013	5.7	2.3	97	5	2.4	102	19.2%	0.30 [0.02, 0.58]	2013
Total (95% CI)			**655**			**456**	**100.0%**	**0.17 [0.01, 0.34]**	

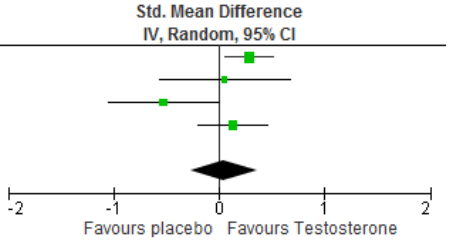
Heterogeneity: Tau² = 0.02; Chi² = 9.24, df = 6 (P = 0.16); I² = 35%
Test for overall effect: Z = 2.08 (P = 0.04)



B) Trials involving men with no major comorbidities

Study or Subgroup	Testosterone Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Steidle 2003	3	1.4	307	2.6	1.4	99	35.0%	0.29 [0.06, 0.51]	2003
Chiang 2009	6.4	1.6	20	6.3	2.4	20	16.2%	0.05 [-0.57, 0.67]	2009
Morales 2009	5	2	29	6.1	2.1	29	19.7%	-0.53 [-1.05, -0.00]	2009
Spitzer 2012	10.5	4.3	70	10	3.2	70	29.1%	0.13 [-0.20, 0.46]	2012
Total (95% CI)			**426**			**218**	**100.0%**	**0.04 [-0.28, 0.36]**	

Heterogeneity: Tau² = 0.06; Chi² = 7.91, df = 3 (P = 0.05); I² = 62%
Test for overall effect: Z = 0.26 (P = 0.80)



eTable6: Libido at end of treatment – Bayesian network meta-analysis

	Standardized mean difference (standard deviation)							
Treatment	**Placebo**	**Patch, 5 mg/d**	**Gel 1%, 50 mg/d**	**Gel 1%, 100 mg/d**	**Gel 2%, 60 mg/d**	**Oral TU, 120 mg/d**	**Oral, TU 160 mg/d**	**IM TU, 1000 mg/ 12 wk**
Patch, 5 mg/d	0.05 (0.16)	—						
Gel 1%, 50 mg/d	0.11 (0.15)	0.06 (0.13)	—					
Gel 1%, 100 mg/d	**0.32 (0.14)**	**0.27 (0.13)**	0.21 (0.12)	—				
Gel 2%, 60 mg/d	0.21 (0.21)	0.16 (0.27)	0.10 (0.26)	-0.11 (0.26)	—			
Oral TU, 120 mg/d	0.45 (0.33)	0.40 (0.37)	0.34 (0.36)	0.13 (0.36)	0.24 (0.39)	—		
Oral TU, 160 mg/d	-0.53 (0.31)	-0.58 (0.35)	-0.64 (0.35)	**-0.85 (0.34)**	-0.74 (0.38)	**-0.98 (0.45)**	—	
IM TU, 1000 mg/12 wk	0.31 (0.22)	0.25 (0.27)	0.19 (0.26)	-0.01 (0.26)	0.10 (0.30)	-0.14 (0.39)	**0.83 (0.38)**	—

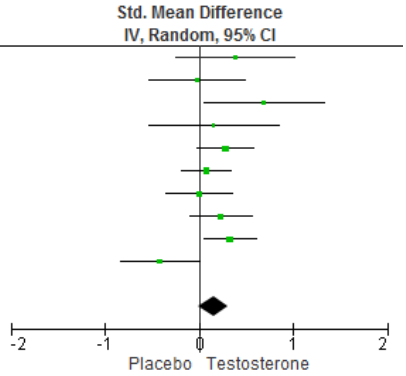
IM = intramuscular injection, TU = testosterone undecanoate.
Note: a positive SMD indicates improved libido. Significant changes are indicated by use of bold and colour (green indicates that the row treatment treatement is significantly better than the column treatment, which red indicates that the row treatment is signigicantly worse than the column treatment).

eFigure4: Individual trial results, erectile function

A) All trials

Study or Subgroup	Testosterone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Cavallini 2004	16	5.8	40	9	4	45		1.41 [0.93, 1.89]	2004
Chiang 2007	21.6	6.8	20	18.1	10.7	20	5.1%	0.38 [-0.24, 1.01]	2007
Morales 2009	11.1	7.7	29	11.3	9.1	29	7.0%	-0.02 [-0.54, 0.49]	2009
Chiang 2009	20.6	6.8	20	15.3	8.2	20	4.9%	0.69 [0.05, 1.33]	2009
Aversa 2010 p. 776	19.5	3	42	19	4	10	4.3%	0.15 [-0.54, 0.84]	2010
Kalinchenko 2010	16.5	7.1	113	14.5	7	71	14.2%	0.28 [-0.02, 0.58]	2010
Jones 2011	15.2	9.7	108	14.4	10.4	112	15.9%	0.08 [-0.19, 0.34]	2011
Ho 2011	16.5	5.9	60	16.5	6	60	11.5%	0.00 [-0.36, 0.36]	2011
Spitzer 2012	21	8.5	70	19	8.5	70	12.6%	0.23 [-0.10, 0.57]	2012
Hackett 2013	14	10.9	97	10.5	10.4	102	15.1%	0.33 [0.05, 0.61]	2013
Gianatti 2014	16	5.925926	43	19	8.15	45	9.3%	-0.42 [-0.84, 0.01]	2014
Total (95% CI)			**602**			**539**	**100.0%**	**0.15 [-0.00, 0.31]**	

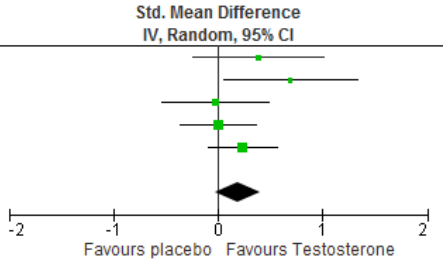
Heterogeneity: Tau² = 0.02; Chi² = 14.07, df = 9 (P = 0.12); I² = 36%
Test for overall effect: Z = 1.91 (P = 0.06)



B) Trials involving men without major comorbidities

Study or Subgroup	Testosterone Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Chiang 2007	21.6	6.8	20	18.1	10.7	20	10.9%	0.38 [-0.24, 1.01]	2007
Chiang 2009	20.6	6.8	20	15.3	8.2	20	10.5%	0.69 [0.05, 1.33]	2009
Morales 2009	11.1	7.7	29	11.3	9.1	29	15.7%	-0.02 [-0.54, 0.49]	2009
Ho 2011	16.5	5.9	60	16.5	6	60	29.6%	0.00 [-0.36, 0.36]	2011
Spitzer 2012	21	8.5	70	19	8.5	70	33.3%	0.23 [-0.10, 0.57]	2012
Total (95% CI)			**199**			**199**	**100.0%**	**0.19 [-0.03, 0.40]**	

Heterogeneity: Tau² = 0.01; Chi² = 4.51, df = 4 (P = 0.34); I² = 11%
Test for overall effect: Z = 1.73 (P = 0.08)



eTable7: Erectile function at end of treatment – Bayesian network meta-analysis

	Standardized mean difference (standard deviation)					
	Placebo	Gel 1%, 50 mg/d	Gel 1%, 100 mg/d	Gel 2%, 60 mg/d	Oral, TU 160 mg/d	IM TU, 1000 mg/12 wk
Gel 1%, 50 mg/d	0.54(0.39)	—				
Gel 1%, 100 mg/d	0.23(0.48)	-0.31(0.62)	—			
Gel 2%, 60 mg/d	0.08(0.47)	-0.46(0.61)	-0.15(0.68)	—		
Oral TU, 160 mg/d	-0.20(0.38)	-0.74(0.55)	-0.43(0.62)	-0.28(0.61)	—	
IM TU, 1000 mg/ 12 wk	0.08(0.22)	-0.46(0.45)	-0.15(0.53)	0.00(0.52)	0.28(0.40)	—

Note: IM = intramuscular injection, TU = testosterone undecanoate.
Note: a positive SMD indicates improved erectile funciton. Significant changes are indicated by use of bold and colour (green indicates that the row treatment treatement is significantly better than the column treatment, which red indicates that the row treatment is signigicantly worse than the column treatment).

eTable 8: Total testosterone level after 3 months of treatment – Bayesian network meta-analysis

	Mean difference (standard deviation)															
	Placebo	Patch 4.8 mg/d	Patch 5 mg/d	Gel 1% 50 mg/d	Gel 1% 75 mg/d	Gel 1% 100 mg/d	Oral TU 120 mg/d	Oral TU 160 mg/d	Pellets 1200 mg	IM TU 1000 mg/ 12 wk	IM TE 100 mg/ wk	IM TE 125 mg/ wk	IM TE 200 mg/ 2 wk	IM TE 250 g/ 3wk	IM TC 200 mg/ 4 wk	Durateston 250 mg/4 wk
Patch 4.8 mg/d	10.12 (5.80)	—														
Patch 5 mg/d	2.53 (1.83)	-7.59 (6.07)	—													
Gel 1% 50 mg/d	**5.32 (1.57)**	-4.79 (6.01)	2.80 (1.79)	—												
Gel 1% 75 mg/d	7.52 (4.19)	-2.59 (7.14)	5.00 (4.57)	2.20 (4.48)	—											
Gel 1% 100 mg/d	**9.61 (1.69)**	-0.51 (6.04)	**7.08 (1.81)**	**4.29 (1.74)**	2.09 (4.51)	—										
Oral TU 120 mg/d	4.35 (3.46)	-5.77 (6.78)	1.82 (3.90)	-0.98 (3.79)	-3.18 (5.44)	-5.26 (3.84)	—									
Oral TU 160 mg/d	-0.03 (3.35)	-10.15 (4.76)	-2.56 (3.79)	-5.35 (3.69)	-7.55 (5.36)	**-9.64 (3.73)**	-4.38 (4.83)	—								
Pellets 1200 mg	**19.60 (5.15)**	**9.48 (4.67)**	**17.07 (5.46)**	**14.28 (5.38)**	12.08 (6.63)	9.99 (5.42)	**15.25 (6.23)**	**19.63 (3.93)**	—							
IM TU 1000 mg/ 12 wk	**8.13 (2.31)**	-1.99 (6.27)	5.60 (2.95)	2.81 (2.80)	0.61 (4.79)	-1.48 (2.87)	3.78 (4.15)	**8.16 (4.09)**	**-11.47 (5.67)**	—						
IM TE 100 mg/wk	**8.67 (3.66)**	-1.45 (6.87)	6.14 (4.09)	3.34 (3.98)	1.15 (5.57)	-0.94 (4.03)	4.32 (5.01)	8.70 (4.94)	-10.93 (6.33)	0.54 (4.33)	—					
IM TE 125 mg/wk	6.79 (5.25)	-3.33 (7.83)	4.26 (5.56)	1.47 (5.48)	-0.73 (6.73)	-2.82 (5.52)	2.44 (6.28)	6.82 (6.24)	-12.81 (7.36)	-1.34 (5.73)	-1.88 (6.39)	—				
IM TE 200 mg/2 wk	6.27 (3.88)	-3.85 (6.99)	3.75 (4.29)	0.95 (4.19)	-1.25 (5.72)	-3.34 (4.25)	1.93 (5.21)	6.30 (5.14)	**-13.33 (6.46)**	-1.86 (4.51)	-2.40 (5.33)	-0.52 (6.49)	—			
IM TE 250 mg/3wk	**10.09 (4.76)**	-0.02 (3.33)	7.57 (5.08)	4.77 (5.00)	2.57 (6.33)	0.48 (5.04)	5.75 (5.90)	**10.12 (3.39)**	**-9.51 (3.28)**	1.96 (5.31)	1.43 (6.01)	3.30 (7.10)	3.82 (6.14)	—		
IM TC 200 mg/4 wk	0.51 (2.88)	-9.61 (6.48)	-2.02 (3.42)	-4.81 (3.29)	-7.01 (5.09)	**-9.10 (3.34)**	-3.84 (4.49)	0.54 (4.42)	**-19.09 (5.90)**	**-7.62 (2.76)**	-8.16 (4.65)	-6.28 (5.99)	-5.76 (4.83)	-9.58 (5.56)	—	
Durateston 250 mg/4 wk	1.12 (3.77)	-9.00 (6.95)	-1.41 (4.20)	-4.21 (4.09)	-6.40 (5.64)	**-8.49 (4.13)**	-3.23 (5.11)	1.15 (5.07)	**-18.48 (6.41)**	**-7.01 (3.34)**	-7.55 (5.25)	-5.67 (6.46)	-5.15 (5.41)	-8.97 (6.09)		—

Note: IM = intramuscular, TC = testosterone cypionate, TE = testosterone enanthate, TU = testosterone undecanoate.

eTable 9: Total testosterone level after 6 months of treatment – Bayesian network meta-analysis

Mean difference (standard deviation)

	Placebo	Patch 4.8 mg/d	Patch 5 mg/d	Gel 1% 50 mg/d	Gel 1% 100 mg/d	Gel 2% 60 mg/d	Gel 2.5% 125 mg/d	Gel 2.5% 25 mg/d (scrotal)	Oral TU 160 mg/d	Oral TU 120 or 160 mg/d	Pellets 1200 mg	IM TU 1000 mg/ 12 wk	IM TE 150 mg /2wk	IM TE 200 mg /2 wk	IM TE 250 g /3wk	IM TE 300 mg /3 wk	IM TE 50-400 mg/wk	IM TC 200 mg /2 wk
Patch 4.8 mg/d	**17.38 (7.17)**	—																
Patch 5 mg/d	8.48 (4.93)	-8.90 (8.75)	—															
Gel 1% 50 mg/d	**8.50 (3.08)**	-8.88 (7.82)	0.02 (5.82)	—														
Gel 1% 100 mg/d	**6.63 (3.01)**	-10.75 (7.78)	-1.84 (5.76)	-1.86 (4.30	—													
Gel 2% 60 mg/d	**18.56 (4.21)**	1.19 (8.29)	10.09 (6.49)	10.07 (5.20)	**11.93 (5.16)**	—												
Gel 2.5% 125 mg/d	12.20 (6.46)	-5.18 (9.67)	3.72 (4.21)	3.70 (7.17)	5.57 (7.12)	-6.36 (7.72)	—											
Gel 2.5% 25 mg/d (scrotal)	7.90 (6.46)	-9.48 (9.70)	-0.58 (4.21)	-0.60 (7.17)	1.27 (7.12)	-10.66 (7.72)	-4.30 (4.21)	—										
Oral TU 160 mg/d	3.51 (2.92)	**-13.87 (6.54)**	-4.97 (5.73)	-4.99 (4.24)	-3.13 (4.18)	**-15.06 (5.10)**	-8.69 (7.09)	-4.39 (7.09)	—									
Oral TU 120 or 160 mg/d	5.66 (4.21)	-11.72 (8.34)	-2.82 (6.49)	-2.84 (5.20)	-0.97 (5.16)	**-12.90 (5.96)**	-6.54 (7.72)	-2.24 (7.71)	2.15 (5.11)	—								
Pellets 1200 mg	6.74 (5.23)	-10.64 (6.12)	-1.74 (7.20)	-1.76 (6.08)	0.11 (6.02)	-11.82 (6.69)	-5.46 (8.31)	-1.16 (8.33)	3.23 (4.34)	1.08 (6.71)	—							
IM TU 1000 mg/12 wk	1.53 (2.95)	**-15.85 (7.43)**	-6.95 (5.73)	-6.97 (4.25)	-5.10 (4.21)	**-17.03 (5.11)**	-10.67 (7.09)	-6.37 (7.09)	-1.98 (3.50)	-4.13 (5.13)	-5.21 (5.58)	—						
IM TE 150 mg/2wk	**12.68 (4.70)**	-4.70 (8.58)	4.21 (6.81)	4.19 (5.61)	6.05 (5.59)	-5.88 (6.31)	0.48 (7.97)	4.79 (7.98)	9.18 (5.54)	7.02 (6.29)	5.95 (7.05)	**11.16 (5.56)**	—					
IM TE 200 mg/2 wk	2.47 (4.44)	-14.91 (8.41)	-6.01 (6.62)	-6.03 (5.41)	-4.17 (5.38)	**-16.09 (6.11)**	-9.73 (7.82)	-5.43 (7.83)	-1.04 (5.29)	-3.19 (6.10)	-4.27 (6.83)	0.94 (5.32)	-10.22 (6.47)	—				
IM TE 250 g/3wk	**12.12 (5.24)**	-5.26 (4.89)	3.64 (7.22)	3.62 (6.08)	5.49 (6.04)	-6.44 (6.70)	-0.08 (8.33)	4.22 (8.35)	**8.61 (4.35)**	6.46 (6.71)	5.38 (3.69)	10.59 (5.60)	-0.56 (7.06)	9.65 (6.84)	—			
IM TE 300 mg/ 3wk	**18.28 (4.73)**	0.91 (8.59)	9.81 (6.83)	9.79 (5.66)	**11.65 (5.61)**	-0.28 (6.32)	6.08 (7.99)	10.39 (8.00)	**14.78 (5.55)**	**12.62 (6.33)**	11.55 (7.01)	**16.76 (5.58)**	5.60 (6.70)	**15.82 (6.49)**	6.16 (7.04)	—		
IM TE 50-400 mg/wk	**14.76 (5.92)**	-2.62 (9.28)	6.29 (7.71)	6.27 (6.68)	8.13 (6.65)	-3.80 (7.26)	2.56 (8.76)	6.87 (8.77)	11.26 (6.60)	9.10 (7.26)	8.03 (7.89)	**13.24 (6.61)**	2.08 (7.56)	12.30 (7.42)	2.64 (7.88)	-3.52 (7.58)	—	
IM TC 200 mg/2 wk	6.62 (5.46)	-10.76 (9.00)	-1.86 (7.38)	-1.88 (6.26)	-0.02 (6.25)	-11.95 (6.90)	-5.58 (8.47)	-1.28 (8.47)	3.11 (6.20)	0.96 (6.88)	-0.12 (7.55)	5.09 (6.21)	-6.07 (7.19)	4.15 (7.00)	-5.50 (7.57)	-11.67 (7.23)	-8.15 (8.08)	—

Note: IM = intramuscular, TC = testosterone cypionate, TE = testosterone enanthate, TU = testosterone undecanoate.

eTable 10: Total testosterone levels at the end of treatment – Bayesian network meta-analysis (2 pages)

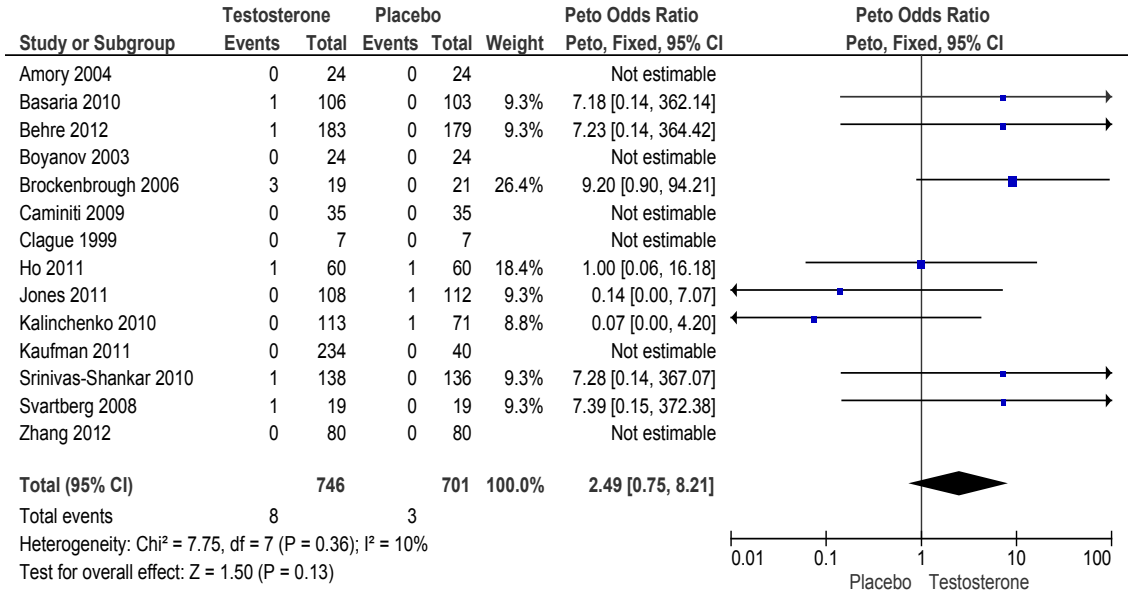
	Mean difference (standard deviation)																										
	Placebo	Patch 4.8 mg/d	Patch 5 mg/d	Gel 1% 5 mg/d	Gel 1% 50 mg/d	Gel 1% 75 mg/d	Gel 1% 100 mg/d	Gel 2% 60 mg/d	Gel 2.5% 125 mg/d	Gel 2.5% 25 mg/d (scrotal)	Oral TU 120 mg/d	Oral TU 160 mg/d	Oral TU 120-160 mg/d	Pellets 1200 mg	IM TU 1000 mg/ 9 wk	IM TU 1000 mg/ 12 wk	IM TE 100 mg/ wk	IM TE 125 mg/ wk	IM TE 150 mg/ 2wk	IM TE 200 mg/ 2 wk	IM TE 250 g/ 3wk	IM TE 300 mg/ 3 wk	IM TE 50-400 mg/ 1-2 wk	IM TC 200 mg/ 2 wk	IM TC 200 mg/ 4 wk	Duratest on 250 mg/4 wk
Patch 4.8 mg/d	7.93 (5.76)	—																									
Patch 5 mg/d	0.57 (1.77)	-7.36 (6.04)	—																								
Gel 1% 5 mg/d	3.69 (4.38)	-4.24 (7.26)	3.12 (4.72)	—																							
Gel 1% 50 mg/d	**4.35 (1.48)**	-3.58 (5.95)	**3.78 (1.89)**	0.66 (4.62)	—																						
Gel 1% 75 mg/d	7.47 (4.71)	-0.46 (7.47)	6.90 (5.03)	3.78 (6.43)	3.12 (4.94)	—																					
Gel 1% 100 mg/d	**7.95 (1.71)**	0.02 (6.02)	**7.39 (1.98)**	4.27 (4.70)	3.61 (1.88)	0.49 (5.01)	—																				
Gel 2% 60 mg/d	**19.77 (4.00)**	11.84 (7.03)	**19.20 (4.37)**	**16.08 (5.94)**	**15.42 (4.27)**	**12.30 (6.19)**	**11.82 (4.35)**	—																			
Gel 2.5% 125 mg/d	4.28 (4.37)	-3.65 (7.23)	3.71 (4.00)	0.59 (6.17)	-0.07 (4.42)	-3.19 (6.39)	-3.68 (4.46)	**-15.49 (5.91)**	—																		
Gel 2.5% 25 mg/d (scrotal)	0.05 (4.36)	-7.88 (7.24)	-0.51 (3.98)	-3.63 (6.17)	-4.29 (4.41)	-7.41 (6.40)	-7.90 (4.45)	**-19.72 (5.91)**	-4.22 (4.01)	—																	
Oral TU 120 mg/d	4.31 (4.07)	-3.62 (7.06)	3.75 (4.44)	0.63 (5.98)	-0.03 (4.33)	-3.15 (6.23)	-3.64 (4.42)	**-15.46 (5.71)**	0.04 (5.97)	4.26 (5.96)	—																
Oral TU 160 mg/d	1.37 (2.08)	-6.56 (5.74)	0.80 (2.74)	-2.32 (4.84)	-2.98 (2.56)	-6.10 (5.15)	**-6.58 (2.70)**	**-18.40 (4.52)**	-2.91 (4.83)	1.32 (4.83)	-2.95 (4.58)	—															
Oral TU 120 or 160 mg/d	5.68 (4.00)	-2.25 (7.01)	5.12 (4.38)	2.00 (5.94)	1.34 (4.27)	-1.78 (6.18)	-2.27 (4.35)	**-14.08 (5.66)**	1.41 (5.94)	5.63 (5.93)	1.37 (5.72)	4.32 (4.51)	—														
Pellets 1200 mg	2.67 (3.78)	-5.26 (5.86)	2.11 (4.18)	-1.01 (5.77)	-1.67 (4.07)	-4.79 (6.04)	-5.28 (4.14)	**-17.09 (5.51)**	-1.60 (5.78)	2.62 (5.76)	-1.64 (5.59)	1.31 (3.55)	-3.01 (5.50)	—													
IM TU 1000 mg/9 wk	**16.24 (5.25)**	8.31 (6.50)	**15.67 (5.55)**	12.55 (6.83)	**11.89 (5.46)**	8.77 (7.07)	8.28 (5.53)	-3.53 (6.64)	11.96 (6.84)	**16.18 (6.83)**	11.92 (6.66)	**14.87 (5.23)**	10.55 (6.61)	**13.56 (5.32)**	—												
IM TU 1000 mg/12 wk	**8.42 (1.37)**	0.49 (5.88)	**7.85 (2.23)**	4.73 (4.59)	**4.07 (2.02)**	0.95 (4.89)	0.46 (2.19)	**-11.35 (4.23)**	4.14 (4.57)	8.36 (4.57)	4.10 (4.29)	**7.05 (2.36)**	2.73 (4.22)	5.74 (3.96)	-7.82 (5.38)	—											
IM TE 100 mg/wk	**9.52 (3.02)**	1.59 (6.52)	**8.95 (3.49)**	5.83 (5.33)	5.17 (3.36)	2.05 (5.58)	1.56 (3.46)	**-10.25 (5.01)**	5.24 (5.29)	9.46 (5.29)	5.20 (5.09)	**8.15 (3.66)**	3.83 (5.04)	6.84 (4.84)	-6.72 (6.06)	1.10 (3.32)	—										
IM TE 125 mg/wk	6.66 (5.41)	-1.27 (7.91)	6.09 (5.68)	2.9 (6.98)	2.31 (5.60)	-0.81 (7.18)	-1.30 (5.66)	-13.11 (6.73)	2.38 (6.98)	6.60 (6.94)	2.34 (6.78)	5.29 (5.79)	0.97 (6.74)	3.98 (6.60)	-9.58 (7.55)	-1.76 (5.58)	-2.86 (6.19)	—									

	Mean difference (standard deviation)																								
	Placebo	Patch 4.8 mg/d	Patch 5 mg/d	Gel 1% 5 mg/d	Gel 1% 50 mg/d	Gel 1% 75 mg/d	Gel 1% 100 mg/d	Gel 2% 60 mg/d	Gel 2.5% 125 mg/d	Gel 2.5% 25 mg/d (scrotal)	Oral TU 120 mg/d	Oral TU 160 mg/d	Oral TU 120-160 mg/d	Pellets 1200 mg	IM TU 1000 mg/ 9 wk	IM TU 1000 mg/ 12 wk	IM TE 100 mg/ wk	IM TE 125 mg/ wk	IM TE 150 mg/ 2wk	IM TE 200 mg/ 2 wk	IM TE 250 g/ 3wk	IM TE 300 mg/ 3 wk	IM TE 50-400 mg/ 1-2 wk	IM TC 200 mg/ 2 wk	IM TC 200 mg/ 4 wk	Durateston 250 mg/4 wk
IM TE 150 mg/2wk	**12.68 (4.59)**	4.75 (7.36)	**12.11 (4.92)**	8.99 (6.31)	8.33 (4.82)	5.21 (6.56)	4.73 (4.90)	-7.09 (6.07)	8.40 (6.33)	**12.62 (6.32)**	8.37 (6.16)	**11.31 (5.03)**	6.99 (6.08)	10.00 (5.92)	-3.56 (6.96)	4.26 (4.78)	3.16 (5.49)	6.02 (7.07)	–							
IM TE 200 mg/ 2wk	**9.16 (2.63)**	1.23 (6.32)	**8.59 (2.78)**	5.47 (5.11)	4.82 (2.91)	1.70 (5.39)	1.21 (3.01)	**-10.61 (4.79)**	4.89 (4.85)	9.11 (4.85)	4.85 (4.85)	**7.79 (3.35)**	3.48 (4.81)	6.49 (4.60)	-7.07 (5.86)	0.75 (2.97)	-0.35 4.00)	2.51 (6.02)	-3.52 (5.30)	–						
IM TE 250 mg/3wk	**8.26 (3.03)**	0.33 (4.92)	**7.69 (3.52)**	4.57 (5.33)	3.92 (3.38)	0.79 (5.60)	0.31 (3.48)	**-11.51 (5.04)**	3.98 (5.33)	8.21 (5.32)	3.95 (5.10)	**6.89 (2.99)**	2.58 (5.03)	5.59 (3.15)	-7.98 (4.28)	-0.15 (3.26)	-1.26 (4.28)	1.61 (6.20)	-4.42 (5.49)	-0.90 (4.01)	–					
IM TE 300 mg/3 wk	**18.24 (4.56)**	10.31 (7.36)	**17.67 (4.89)**	**14.55 (6.33)**	**13.89 (4.80)**	10.77 (6.58)	**10.28 (4.87)**	-1.53 (6.07)	**13.96 (6.31)**	**18.18 (6.32)**	**13.92 (6.11)**	**16.87 (5.01)**	**12.55 (6.07)**	**15.56 (5.93)**	2.00 (6.96)	**9.82 (4.76)**	8.72 (5.47)	11.58 (7.06)	5.56 (6.48)	9.07 (5.26)	9.97 (5.49)	–				
IM TE 50-400 mg/1-2 wk	**14.73 (5.81)**	6.80 (8.18)	**14.16 (6.06)**	11.04 (7.27)	10.39 (5.98)	7.27 (7.48)	6.78 (6.06)	-5.04 (7.06)	10.45 (7.26)	**14.68 (7.26)**	10.42 (7.09)	**13.36 (6.16)**	9.05 (7.04)	12.06 (6.95)	-1.51 (7.84)	6.32 (5.96)	5.22 (6.54)	8.08 (7.95)	2.05 (7.44)	5.57 (6.39)	6.47 (6.56)	-3.50 (7.39)	–			
IM TC 200 mg/2 wk	3.21 (4.75)	-4.72 (7.45)	2.64 (5.06)	-0.48 (6.43)	-1.14 (4.97)	-4.26 (6.69)	-4.75 (5.05)	**-16.56 (6.22)**	-1.07 (6.45)	3.15 (6.45)	-1.11 (6.24)	1.84 (5.18)	-2.48 (6.22)	0.53 (6.07)	-13.03 (7.09)	-5.21 (4.94)	-6.31 (5.63)	-3.45 (7.21)	-9.47 (6.60)	-5.96 (5.43)	-5.05 (5.64)	**-15.03 (6.57)**	-11.52 (7.51)	–		
IM TC 200 mg/4 wk	1.36 (4.29)	-6.57 (7.13)	0.79 (4.63)	-2.33 (6.12)	-2.99 (4.54)	-6.11 (6.37)	-6.60 (4.60)	**-18.41 (5.85)**	-2.92 (6.12)	1.30 (6.12)	-2.96 (5.90)	-0.01 (4.70)	-4.33 (5.87)	-1.32 (5.67)	**-14.88 (6.73)**	-7.06 (4.06)	-8.16 (5.24)	-5.30 (6.91)	-11.32 (6.26)	-7.81 (5.02)	-6.91 (5.19)	**-16.88 (6.24)**	-13.38 (7.21)	-1.85 (6.40)	–	
Durateston 250 mg/4 wk	1.61 (4.35)	-6.32 (7.16)	1.05 (4.70)	-2.07 (6.18)	-2.73 (4.59)	-5.85 (6.41)	-6.34 (4.66)	**-18.15 (5.91)**	-2.66 (6.16)	1.56 (6.16)	-2.70 (5.95)	0.25 (4.76)	-4.07 (5.90)	-1.06 (5.71)	**-14.62 (6.77)**	-6.80 (4.13)	-7.90 (5.29)	-5.04 (6.93)	-11.06 (6.32)	-7.55 (5.08)	-6.65 (5.25)	**-16.62 (6.29)**	-13.12 (7.27)	-1.59 (6.42)	0.26 (4.09)	–

Note: IM = intramuscular, TC = testosterone cypionate, TE = testosterone enanthate, TU = testosterone undecanoate.

Supplemental Online Content: Elliott et al. Testosterone therapy in hypogonadal men: a systematic review and network meta-analysis.

eFigure 5: Odds of cardiovascular death associated with the use of any testosterone v. placebo



Study or Subgroup	Testosterone Events	Total	Placebo Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Amory 2004	0	24	0	24		Not estimable
Basaria 2010	1	106	0	103	9.3%	7.18 [0.14, 362.14]
Behre 2012	1	183	0	179	9.3%	7.23 [0.14, 364.42]
Boyanov 2003	0	24	0	24		Not estimable
Brockenbrough 2006	3	19	0	21	26.4%	9.20 [0.90, 94.21]
Caminiti 2009	0	35	0	35		Not estimable
Clague 1999	0	7	0	7		Not estimable
Ho 2011	1	60	1	60	18.4%	1.00 [0.06, 16.18]
Jones 2011	0	108	1	112	9.3%	0.14 [0.00, 7.07]
Kalinchenko 2010	0	113	1	71	8.8%	0.07 [0.00, 4.20]
Kaufman 2011	0	234	0	40		Not estimable
Srinivas-Shankar 2010	1	138	0	136	9.3%	7.28 [0.14, 367.07]
Svartberg 2008	1	19	0	19	9.3%	7.39 [0.15, 372.38]
Zhang 2012	0	80	0	80		Not estimable
Total (95% CI)		**746**		**701**	**100.0%**	**2.49 [0.75, 8.21]**
Total events	8		3			

Heterogeneity: Chi² = 7.75, df = 7 (P = 0.36); I² = 10%

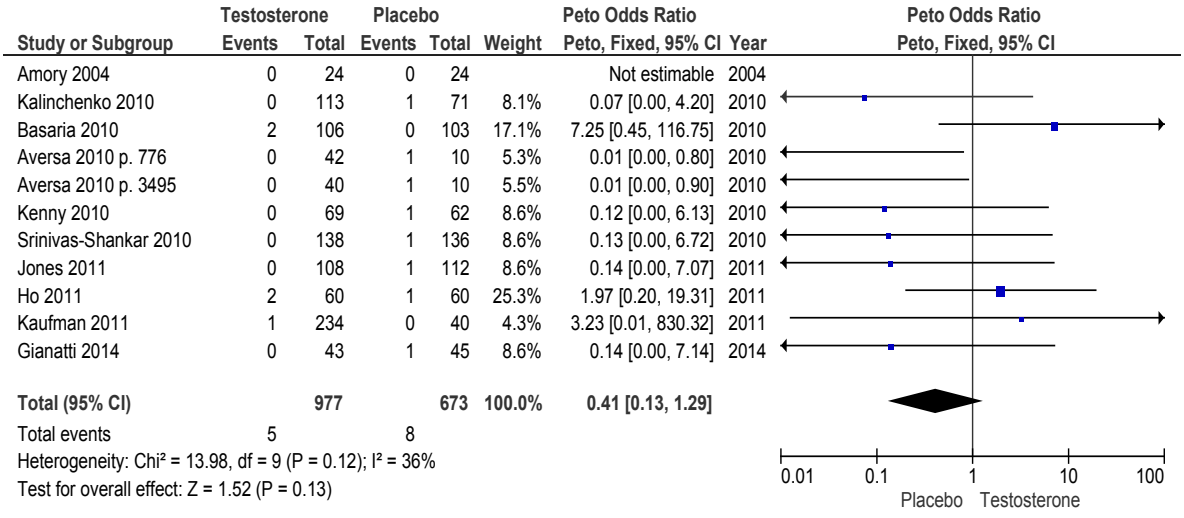
Test for overall effect: Z = 1.50 (P = 0.13)

eTable 11: Odds of cardiovascular death associated with individual testosterone products – Bayesian network meta-analysis

	Odds ratio (95% credible interval)*									
	Placebo	Gel 1%, 50 mg/d	Gel 1%, 100 mg/d	Gel 1.62%, 40 mg/d	Gel 2%, 60 mg/d	Oral TU 120 mg/d	Oral TU, T-based dose†	IM TU, 1000 mg/12wk	IM TE, 200 mg/2 wk	IM TE, 250 mg/3 wk
Gel 1%, 50 mg/d	1.98 (0.44, 9.16)	—								
Gel 1%, 100 mg/d	1.51 (0.11, 25.19)	0.76 (0.04, 18.25)	—							
Gel 1.62%, 40 mg/d	0.38 (0.02, 11.14)	0.19 (0.01, 7.39)	0.25 (0.00, 17.36)	—						
Gel 2%, 60 mg/d	0.26 (0.01, 3.60)	0.13 (0.00, 2.79)	0.16 (0.00, 7.02)	0.65 (0.00, 44.60)	—					
Oral TU 120 mg/d	0.52 (0.01, 12.71)	0.26 (0.00, 8.93)	0.34 (0.00, 22.19)	1.35 (0.01, 108.20)	2.07 (0.02, 208.90)	—				
Oral TU, T-based dose†	0.48 (0.01, 10.85)	0.24 (0.00, 7.97)	0.30 (0.00, 18.93)	1.17 (0.01, 106.60)	1.88 (0.02, 184.90)	0.90 (0.01, 128.10)	—			
IM TU, 1000 mg/12 wk	0.66 (0.15, 2.74)	0.34 (0.04, 2.64)	0.43 (0.02, 8.81)	1.73 (0.04, 56.03)	2.58 (0.12, 99.44)	1.27 (0.04, 63.46)	1.40 (0.04, 85.15)	—		
IM TE, 200 mg /2 wk	0.59 (0.03, 6.12)	0.29 (0.01, 5.57)	0.38 (0.01, 13.00)	1.40 (0.02, 81.67)	2.19 (0.04, 160.80)	1.11 (0.01, 91.06)	1.20 (0.02, 114.80)	0.86 (0.04, 14.99)	—	
IM TE, 250 mg /3 wk	0.45 (0.01, 14.09)	0.22 (0.00, 9.35)	0.29 (0.00, 19.59)	1.19 (0.01, 113.90)	1.77 (0.02, 224.00)	0.86 (0.01, 140.20)	0.97 (0.01, 151.30)	0.68 (0.02, 18.53)	0.79 (0.01, 60.90)	—

Note: IM = intramuscular injection, TC = testosterone cypionate, TE = testosterone enanthate, TU = testosterone undecanoate.
Odds ratios greater than one indicate that the treatment specified in the row has a higher odds of an event than the column treatment. Bold results indicate statistical significance.
*Random-effects model.
†Oral TU dose based on testosterone levels at baseline. Patients with total testosterone < 8 nmol/L received 120 mg/d; patients with total testosterone between 8 and 12 nmol/L received 160 mg/d (data not reported by dose).

eFigure 6: Odds of myocardial infarction associated with the use of any testosterone v. placebo

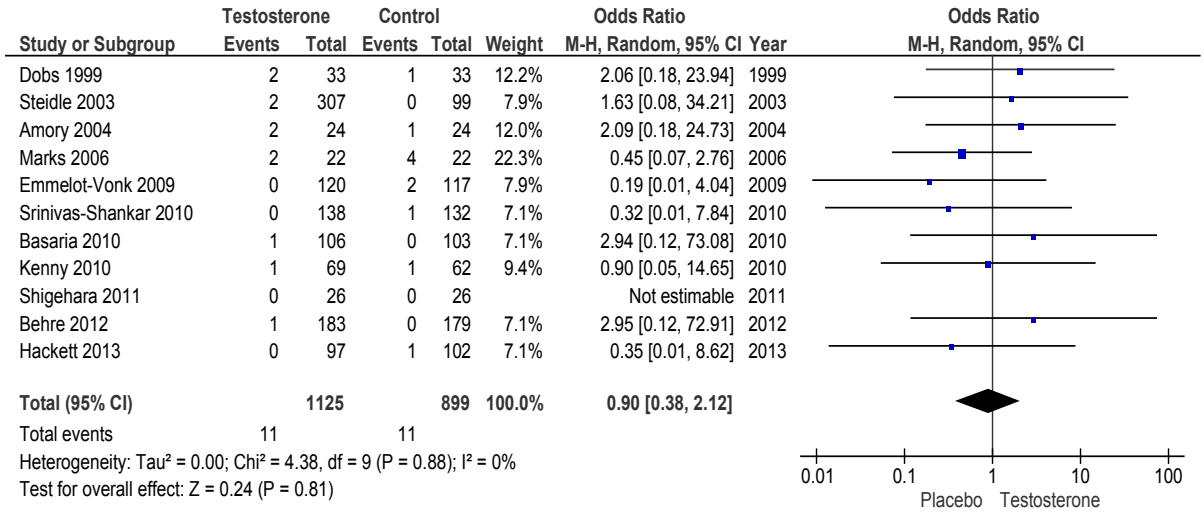


eTable 12: Odds of myocardial infarction associated with individual testosterone products – Bayesian network meta-analysis

	Odds ratio (95% credible interval)								
	Placebo	Gel 1%, 5 mg/d	Gel 1%, 50 mg/d	Gel 1 %, 100 mg/d	Gel 1.62%, 40 mg/d	Gel 2% 60 mg/d	Oral TU 160 mg/d	IM TU, 1000 mg/12wk	IM TE, 200 mg/2 wk
Gel 1%, 5 mg/d	0.25 (0.01, 3.97)	—							
Gel 1%, 50 mg/d	0.26 (0.01, 3.79)	1.00 (0.01, 103.70)	—						
Gel 1%, 100 mg/d	2.54 (0.25, 32.45)	10.67 (0.27, 827.90)	10.83 (0.27, 822.70)	—					
Gel 1.62%, 40 mg/d	0.78 (0.05, 20.17)	3.44 (0.07, 315.70)	3.28 (0.06, 446.90)	0.32 (0.01, 16.31)	—				
Gel 2%, 60 mg/d	0.26 (0.01, 3.98)	1.04 (0.01, 92.63)	1.03 (0.01, 101.50)	0.10 (0.00, 3.86)	0.31 (0.00, 16.20)	—			
Oral TU 160 mg/d	0.24 (0.00, 5.52)	0.95 (0.00, 140.30)	0.95 (0.00, 115.90)	0.09 (0.00, 4.95)	0.29 (0.00, 22.33)	0.90 (0.00, 98.30)	—		
IM TU, 1000 mg/12 wk	0.46 (0.12, 1.49)	1.82 (0.09, 87.08)	1.81 (0.09, 92.19)	0.17 (0.01, 2.53)	0.58 (0.02, 12.42)	1.73 (0.08, 78.66)	1.88 (0.08, 191.00)	—	
IM TE, 200 mg/2 wk	0.55 (0.01, 15.52)	2.18 (0.02, 313.50)	2.21 (0.02, 282.20)	0.20 (0.00, 12.36)	0.65 (0.00, 51.47)	2.07 (0.02, 275.60)	2.26 (0.01, 543.40)	1.21 (0.02, 43.64)	—

Note: IM = intramuscular injection, TE = testosterone enanthate, TU = testosterone undecanoate.

eFigure 7: Odds of prostate cancer associated with the use of any testosterone v. placebo



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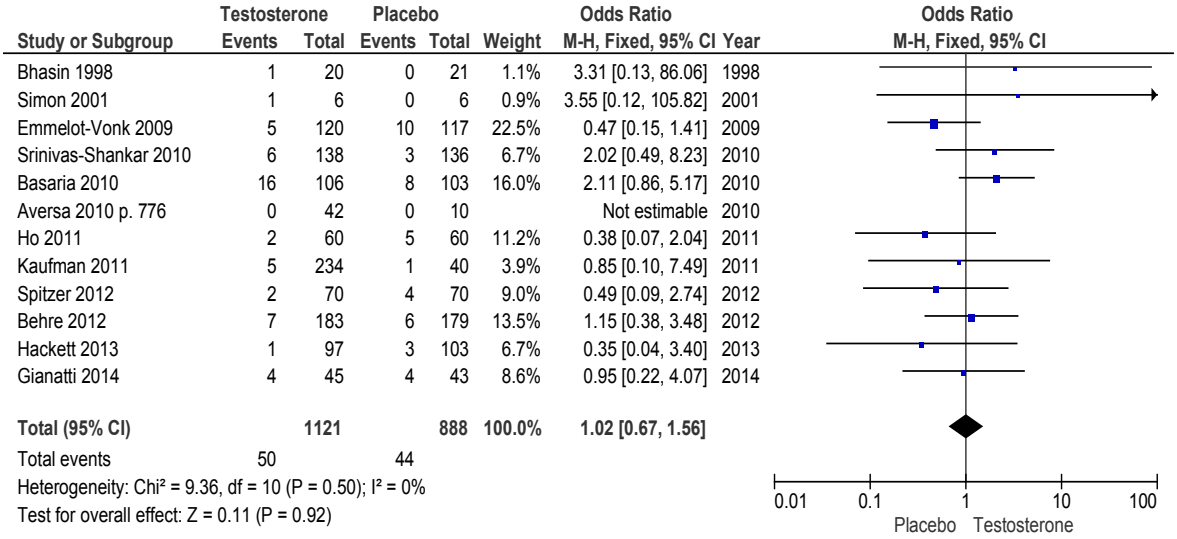
eTable 13: Odds of prostate cancer associated with individual testosterone products – Bayesian network meta-analysis

	Odds ratio (95% credible interval)									
	Placebo	Patch 5 mg/d	Gel 1%, 5 mg/d	Gel 1% 50 mg/d	Gel 1%, 100 mg/d	Oral TU 160 mg/d	IM TU, 1000 mg/12wk	IM TE, 150 mg/2wk	IM TE, 200 mg/2 wk	IM TE, 250 mg/4 wk
Patch 5 mg/d	2.66 (0.37, 19.15)	—								
Gel 1%, 5 mg/d	0.65 (0.04, 8.54)	0.24 (0.01, 6.40)	—							
Gel 1% 50 mg/d	0.53 (0.08, 2.89)	0.20 (0.02, 2.08)	0.82 (0.03, 22.64)	—						
Gel 1%, 100 mg/d	0.80 (0.09, 5.48)	0.30 (0.02, 3.30)	1.23 (0.05, 39.26)	1.51 (0.11, 21.44)	—					
Oral TU 160 mg/d	0.17 (0.01, 2.16)	0.06 (0.00, 1.48)	0.26 (0.00, 10.95)	0.31 (0.01, 7.99)	0.21 (0.00, 6.28)	—				
IM TU, 1000 mg/12 wk	0.28 (0.01, 4.07)	0.10 (0.00, 2.79)	0.41 (0.01, 23.54)	0.52 (0.01, 12.50)	0.34 (0.01, 11.36)	1.61 (0.02, 119.70)	—			
IM TE, 150 mg/2wk	0.43 (0.05, 2.84)	0.16 (0.01, 2.38)	0.67 (0.02, 21.26)	0.80 (0.05, 11.61)	0.54 (0.03, 9.83)	2.53 (0.10, 114.40)	1.55 (0.05, 77.57)	—		
IM TE, 200 mg/2 wk	2.36 (0.35, 18.33)	0.90 (0.12, 7.18)	3.83 (0.14, 118.00)	4.51 (0.39, 66.58)	2.96 (0.23, 52.73)	14.36 (0.58, 690.30)	8.80 (0.31, 451.50)	5.73 (0.38, 93.03)	—	
IM TE, 250 mg/4 wk	0.61 (0.01, 15.70)	0.23 (0.00, 10.32)	1.01 (0.01, 76.71)	1.16 (0.02, 48.15)	0.78 (0.01, 39.09)	3.68 (0.04, 334.90)	2.28 (0.02, 244.50)	1.44 (0.02, 68.34)	0.25 (0.00, 10.89)	—

Note: IM = intramuscular injection, TE = testosterone enanthate, TU = testosterone undecanoate.

eFigure 8: Odds of serious adverse events associated with the use of any testosterone v. placebo



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eTable 14: Odds of serious adverse events associated with individual testosterone products – Bayesian network meta-analysis

	Odds ratio (95% credible interval)									
	Placebo	Patch, 5 mg/d	Gel 1%, 50 mg/d	Gel 1%, 100 mg/d	Gel 1%, 125 mg/d	Gel 1.62%, 40.5 mg/d	Oral TU 160 mg/d	IM TU, 1000 mg/9 wk	IM TU, 1000 mg/12 wk	IM TE, 250 mg/3 wk
Patch, 5 mg/d	1.29 (0.13, 14.21)	—								
Gel 1%, 50 mg/d	1.36 (0.49, 3.84)	1.06 (0.08, 12.44)	—							
Gel 1%, 100 mg/d	1.37 (0.49, 3.48)	1.05 (0.08, 12.61)	1.00 (0.23, 4.04)	—						
Gel 1%, 125 mg/d	2.26 (0.12, 50.44)	1.69 (0.04, 86.86)	1.64 (0.07, 42.10)	1.65 (0.08, 44.43)	—					
Gel 1.62%, 40.5 mg/d	0.79 (0.12, 8.05)	0.62 (0.03, 16.54)	0.58 (0.07, 7.12)	0.58 (0.07, 7.63)	0.37 (0.01, 15.61)	—				
Oral TU 160 mg/d	0.45 (0.12, 1.60)	0.35 (0.02, 4.71)	0.33 (0.06, 1.66)	0.33 (0.06, 1.66)	0.20 (0.01, 4.65)	0.56 (0.04, 5.78)	—			
IM TU, 1000 mg/9 wk	2.83 (0.08, 193.70)	2.11 (0.07, 116.90)	2.02 (0.05, 152.20)	2.09 (0.05, 161.10)	1.28 (0.01, 223.60)	3.45 (0.05, 356.40)	6.25 (0.13, 524.50)	—		
IM TU,1000 mg/12 wk	0.50 (0.17, 1.36)	0.39 (0.03, 4.46)	0.36 (0.08, 1.54)	0.36 (0.09, 1.55)	0.22 (0.01, 4.76)	0.61 (0.05, 5.28)	1.09 (0.22, 5.65)	0.17 (0.00, 6.57)	—	
IM TE, 250 mg/3 wk	1.89 (0.15, 26.54)	1.48 (0.28, 6.32)	1.36 (0.09, 22.83)	1.39 (0.09, 23.37)	0.83 (0.01, 50.46)	2.31 (0.08, 64.42)	4.28 (0.24, 82.89)	0.70 (0.01, 16.17)	3.80 (0.26, 67.67)	—

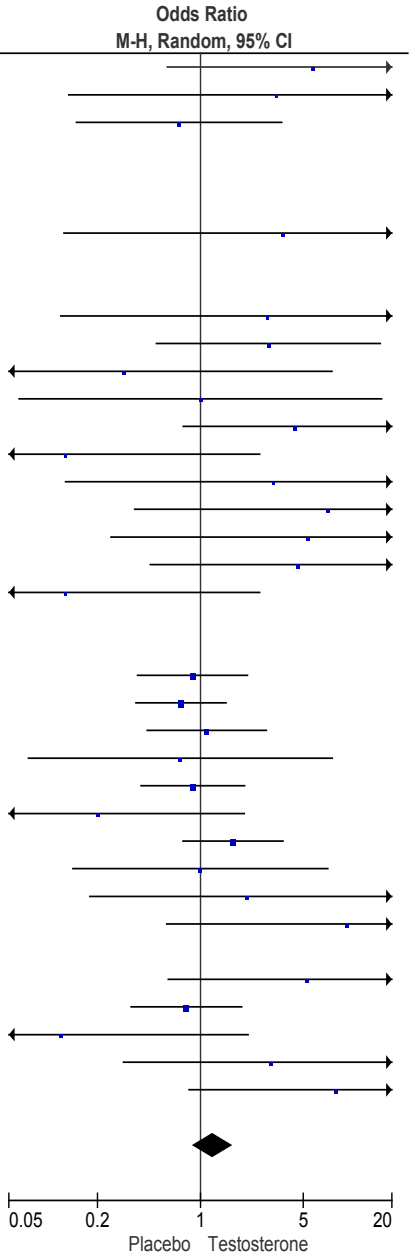
Note: IM = intramuscular injection, TE = testosterone enanthate, TU = testosterone undecanoate.

eFigure 9: Odds of withdrawals due to adverse events associated with the use of any testosterone v. placebo

Study or Subgroup	Testosterone Events	Testosterone Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Sih 1997	5	17	1	15	1.8%	5.83 [0.60, 57.10]	1997
Bhasin 1998	1	20	0	21	0.9%	3.31 [0.13, 86.06]	1998
Grinspoon 1998	3	26	4	26	3.4%	0.72 [0.14, 3.58]	1998
Clague 1999	0	7	0	7		Not estimable	1999
Bhasin 2000	0	17	0	14		Not estimable	2000
Ferrando 2003	0	7	0	5		Not estimable	2003
Tan 2003	1	5	0	5	0.8%	3.67 [0.12, 113.73]	2003
Boyanov 2003	0	24	0	24		Not estimable	2003
Cavallini 2004	0	40	0	45		Not estimable	2004
Shabsigh 2004	1	39	0	36	0.9%	2.84 [0.11, 72.08]	2004
Amory 2004	5	24	2	24	2.9%	2.89 [0.50, 16.67]	2004
Merza 2005	0	20	1	19	0.9%	0.30 [0.01, 7.85]	2005
Marks 2006	1	22	1	22	1.2%	1.00 [0.06, 17.07]	2006
Brockenbrough 2006	6	19	2	21	3.0%	4.38 [0.76, 25.20]	2006
Chiang 2007	0	20	3	20	1.0%	0.12 [0.01, 2.53]	2007
Svartberg 2008	1	19	0	19	0.9%	3.16 [0.12, 82.64]	2008
Basurto 2008	3	25	0	23	1.0%	7.31 [0.36, 149.67]	2008
Morales 2009	2	29	0	29	1.0%	5.36 [0.25, 116.76]	2009
Shores 2009	4	17	1	16	1.7%	4.62 [0.46, 46.67]	2009
Chiang 2009	0	20	3	20	1.0%	0.12 [0.01, 2.53]	2009
Caminiti 2009	0	35	0	35		Not estimable	2009
Heufelder 2009	0	16	0	16		Not estimable	2009
Emmelot-Vonk 2009	11	120	12	117	9.7%	0.88 [0.37, 2.09]	2009
Kenny 2010	24	69	26	62	12.7%	0.74 [0.36, 1.50]	2010
Srinivas-Shankar 2010	10	138	9	136	8.6%	1.10 [0.43, 2.80]	2010
Aversa 2010 p. 3495	3	40	1	10	1.7%	0.73 [0.07, 7.87]	2010
Basaria 2010	13	106	14	103	10.6%	0.89 [0.40, 2.00]	2010
Kalinchenko 2010	1	113	3	71	1.8%	0.20 [0.02, 1.98]	2010
Jones 2011	18	108	12	112	11.1%	1.67 [0.76, 3.65]	2011
Ho 2011	2	60	2	60	2.3%	1.00 [0.14, 7.34]	2011
Shigehara 2011	2	26	1	26	1.6%	2.08 [0.18, 24.51]	2011
Kaufman 2011	25	234	0	40	1.2%	9.86 [0.59, 165.24]	2011
Zhang 2012	0	80	0	80		Not estimable	2012
Spitzer 2012	5	70	1	70	2.0%	5.31 [0.60, 46.65]	2012
Behre 2012	10	183	12	179	9.6%	0.80 [0.34, 1.91]	2012
Hackett 2013	0	97	4	102	1.1%	0.11 [0.01, 2.11]	2013
Gianatti 2014	3	45	1	43	1.8%	3.00 [0.30, 30.02]	2014
Borst 2014	5	14	1	16	1.8%	8.33 [0.84, 83.17]	2014
Total (95% CI)		**1971**		**1689**	**100.0%**	**1.22 [0.89, 1.67]**	
Total events	165		117				

Heterogeneity: Tau² = 0.07; Chi² = 32.29, df = 29 (P = 0.31); I² = 10%

Test for overall effect: Z = 1.24 (P = 0.22)



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eTable 15: Odds of withdrawals due to adverse events – Bayesian network meta-analysis

Odds ratio (95% credible interval)

	Placebo	Patch, 5 mg/d	Gel 1%, 5 mg/d	Gel 1%, 50 mg/d	Gel 1%, 75 mg/d	Gel 1%, 100 mg/d	Gel 1.62%, 40.5 mg/d	Gel 2%, 60 mg/d	Oral TU 120 mg/d	Oral TU 160 mg/d	Oral TU 120-160 mg/d	IM TU, 1000 mg/9 wk	IM TU, 1000 mg/12 wk	IM TE, 100 mg/ wk	IM TE, 125 mg/ wk	IM TE, 150 mg/ 2 wk	IM TE, 200 mg/ 2 wk	IM TE, 250 mg/ 3 wk	IM TE, 250 mg/ 4 wk	IM TE, 300 mg/ 3 wk	IM TE, 50-400 mg/wk	IM TC, 200 mg/ 2 wk
Patch, 5 mg/d	2.49 (0.77, 7.59)	—																				
Gel 1%, 5 mg/d	0.82 (0.31, 2.30)	0.33 (0.08, 1.62)	—																			
Gel 1%, 50 mg/d	0.89 (0.46, 1.64)	0.35 (0.11, 1.15)	1.08 (0.31, 3.32)	—																		
Gel 1%, 75 mg/d	3.36 (0.45, 35.75)	1.36 (0.13, 18.27)	4.14 (0.42, 51.50)	3.83 (0.47, 44.57)	—																	
Gel 1%, 100 mg/d	0.81 (0.33, 1.84)	0.33 (0.09, 1.09)	0.99 (0.24, 3.46)	0.91 (0.33, 2.45)	0.24 (0.02, 2.08)	—																
Gel 1.62%, 40.5 mg/d	**11.90 (1.36, 238.20)**	4.75 (0.40, 114.80)	**14.51 (1.28, 344.40)**	**13.47 (1.38, 280.10)**	3.54 (0.16, 126.10)	**15.01 (1.43, 332.00)**	—															
Gel 2%, 60 mg/d	1.64 (0.53, 5.04)	0.65 (0.14, 3.31)	2.00 (0.43, 8.47)	1.86 (0.52, 6.87)	0.49 (0.04, 4.94)	2.02 (0.52, 8.57)	0.14 (0.01, 1.60)	—														
Oral TU 120 mg/d	0.59 (0.01, 13.06)	0.24 (0.00, 6.41)	0.71 (0.01, 18.50)	0.67 (0.01, 15.76)	0.16 (0.00, 7.20)	0.74 (0.01, 18.77)	0.05 (0.00, 2.33)	0.36 (0.01, 10.04)	—													
Oral TU 160 mg/d	1.02 (0.38, 2.87)	0.41 (0.09, 2.04)	1.24 (0.30, 5.04)	1.15 (0.36, 3.96)	0.30 (0.02, 2.91)	1.26 (0.35, 5.05)	**0.09 (0.00, 0.94)**	0.62 (0.14, 2.91)	1.76 (0.07, 91.80)	—												
Oral TU 120-160 mg/d	0.54 (0.01, 12.85)	0.21 (0.00, 6.62)	0.65 (0.01, 17.48)	0.61 (0.01, 15.60)	0.15 (0.00, 6.99)	0.66 (0.01, 18.43)	0.04 (0.00, 2.27)	0.32 (0.01, 9.67)	0.92 (0.01, 127.20)	0.54 (0.01, 13.83)	—											
IM TU, 1000 mg/9 wk	4.35 (0.10, 216.80)	1.76 (0.03, 90.23)	5.25 (0.11, 289.70)	4.97 (0.11, 250.40)	1.22 (0.02, 109.40)	5.46 (0.11, 288.70)	0.35 (0.00, 29.21)	2.64 (0.05, 152.30)	7.67 (0.06, 1506.00)	4.27 (0.09, 239.50)	8.30 (0.06, 1647.00)	—										
IM TU,	0.58	0.23	0.70	0.66	0.17	0.72	**0.05**	0.36	0.98	0.57	1.10	0.13	—									

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1000 mg/12 wk	(0.24, 1.40)	(0.06, 1.01)	(0.18, 2.60)	(0.22, 1.97)	(0.01, 1.63)	(0.21, 2.54)	**(0.00, 0.53)**	(0.08, 1.48)	(0.04, 51.60)	(0.14, 2.11)	(0.04, 57.89)	(0.00, 6.40)										
IM TE, 100 mg/ wk	0.54 (0.01, 12.88)	0.22 (0.00, 6.51)	0.65 (0.02, 17.35)	0.61 (0.01, 15.67)	0.16 (0.00, 6.61)	0.67 (0.02, 18.30)	0.04 (0.00, 2.21)	0.33 (0.01, 9.84)	1.00 (0.01, 128.50)	0.53 (0.01, 13.77)	1.05 (0.01, 146.80)	0.13 (0.00, 18.13)	0.92 (0.02, 25.90)	—								
IM TE, 125 mg/ wk	5.83 (0.82, 59.03)	2.38 (0.23, 31.20)	7.06 (0.77, 87.97)	6.62 (0.83, 71.43)	1.72 (0.08, 36.85)	7.26 (0.87, 85.03)	0.49 (0.01, 11.06)	3.63 (0.36, 45.87)	10.53 (0.24, 888.60)	5.77 (0.62, 70.45)	11.41 (0.26, 1046. 00)	1.44 (0.02, 116.00)	**10.15 (1.15, 121.50)**	11.12 (0.28, 749.80)	—							
IM TE, 150 mg/ 2 wk	0.73 (0.04, 11.62)	0.30 (0.01, 6.15)	0.88 (0.04, 16.24)	0.83 (0.04, 14.96)	0.21 (0.01, 6.61)	0.91 (0.04, 16.84)	0.06 (0.00, 2.09)	0.45 (0.02, 8.82)	1.27 (0.02, 138.10)	0.70 (0.03, 13.87)	1.35 (0.02, 198.20)	0.17 (0.00, 16.70)	1.25 (0.06, 23.16)	1.36 (0.02, 112.70)	0.12 (0.00, 3.87)	—						
IM TE, 200 mg/ 2 wk	2.46 (0.68, 9.07)	0.99 (0.21, 4.92)	2.99 (0.58, 14.90)	2.82 (0.68, 11.63)	0.72 (0.05, 8.33)	3.06 (0.67, 14.12)	0.20 (0.01, 2.81)	1.51 (0.26, 8.58)	4.22 (0.15, 236.10)	2.46 (0.43, 12.16)	4.65 (0.16, 306.60)	0.58 (0.01, 32.69)	4.24 (0.85, 20.95)	4.50 (0.15, 234.00)	0.41 (0.03, 4.36)	3.39 (0.15, 87.72)	—					
IM TE, 250 mg/ 3 wk	3.27 (0.41, 36.78)	1.34 (0.12, 17.27)	3.99 (0.39, 52.51)	3.71 (0.43, 45.28)	0.95 (0.04, 24.35)	4.07 (0.45, 52.84)	0.27 (0.01, 6.95)	2.03 (0.19, 28.16)	5.93 (0.14, 472.00)	3.19 (0.32, 43.45)	6.40 (0.15, 489.60)	0.84 (0.02, 24.45)	5.68 (0.61, 68.98)	6.47 (0.12, 444.40)	0.56 (0.03, 12.07)	4.69 (0.15, 184.90)	1.34 (0.11, 20.43)	—				
IM TE, 250 mg/ 4 wk	1.58 (0.16, 20.06)	0.64 (0.05, 9.46)	1.92 (0.15, 27.79)	1.78 (0.17, 23.45)	0.47 (0.02, 11.42)	1.99 (0.16, 28.78)	0.13 (0.00, 4.19)	0.97 (0.07, 15.72)	2.78 (0.06, 245.90)	1.54 (0.12, 23.50)	3.00 (0.06, 303.70)	0.37 (0.00, 34.67)	2.74 (0.23, 39.08)	2.96 (0.05, 226.90)	0.26 (0.01, 6.49)	2.16 (0.06, 113.10)	0.64 (0.05, 10.13)	0.46 (0.02, 12.74)	—			
IM TE, 300 mg/ 3 wk	0.64 (0.10, 3.67)	0.25 (0.03, 2.15)	0.78 (0.09, 5.84)	0.73 (0.10, 4.67)	0.19 (0.01, 2.80)	0.79 (0.11, 5.72)	0.05 (0.00, 0.94)	0.39 (0.05, 3.10)	1.10 (0.03, 76.10)	0.63 (0.07, 4.76)	1.19 (0.03, 91.15)	0.15 (0.00, 9.35)	1.11 (0.14, 8.01)	1.16 (0.03, 71.09)	0.11 (0.01, 1.52)	0.86 (0.03, 28.80)	0.26 (0.03, 2.26)	0.19 (0.01, 3.00)	0.40 (0.02, 7.60)	—		
IM TE, 50-400 mg/wk	0.59 (0.02, 20.23)	0.24 (0.01, 10.43)	0.72 (0.02, 28.40)	0.67 (0.02, 24.91)	0.18 (0.00, 9.83)	0.74 (0.02, 29.62)	0.05 (0.00, 3.85)	0.36 (0.01, 14.89)	1.07 (0.01, 176.50)	0.57 (0.01, 22.02)	1.18 (0.01, 183.10)	0.15 (0.00, 20.10)	1.04 (0.02, 37.24)	1.10 (0.01, 144.00)	0.10 (0.00, 5.80)	0.84 (0.01, 89.72)	0.24 (0.00, 10.61)	0.18 (0.00, 10.17)	0.37 (0.00, 25.46)	0.89 (0.02, 49.28)	—	
IM TC, 200 mg/ 2 wk	4.53 (0.63, 45.05)	1.83 (0.18, 24.63)	5.54 (0.60, 64.27)	5.15 (0.66, 57.15)	1.35 (0.06, 28.17)	5.63 (0.65, 66.84)	0.38 (0.01, 8.13)	2.79 (0.29, 35.35)	7.98 (0.20, 634.50)	4.47 (0.48, 52.87)	8.65 (0.20, 790.50)	1.07 (0.01, 89.58)	7.84 (0.91, 93.43)	8.70 (0.19, 561.30)	0.77 (0.04, 16.81)	6.52 (0.21, 223.50)	1.88 (0.17, 25.72)	1.40 (0.06, 27.58)	2.87 (0.12, 71.94)	7.22 (0.50, 127.30)	7.76 (0.13, 617.30)	—

Note: IM = intramuscular injection, TC = testosterone cypionate, TE = testosterone enanthate, TU = testosterone undecanoate.

Supplemental Online Content: Elliott et al. Testosterone therapy in hypogonadal men: a systematic review and network meta-analysis.

eTable 16: Summary of harms outcomes reported in non-randomized studies

Study	Population	Treatment (no. in group)	Outcome	Comments
Retrospective cohort				
Vigen 2013	Men who underwent coronary angiography at a VA medical centre	• No treatment (7486) • TRT, dose NR (1223) Mean follow-up: 840 d	• Cardiovascular events*: HR 1.37, 95% CI 1.21 to 1.56	Entry into cohort was based on filling a prescription for TRT (patch, gel, injectable; brands NR). Data reported as TRT v. no TRT. Length of follow-up differed by group.
Shores 2012	> 40 yr treated at a VA medical center, inpatient or outpatient	• No treatment (633) • TRT (398) Duration: 20.2 mo	• Prostate cancer: No treatment: 13/633 men; TRT: 7/398 men	Data reported as TRT v. no TRT. TRTs included injectable, patch, or gel (brands NR)
Rhoden 2006	Hypogonadal men with negative prostate biopsy prior to starting TRT	• IM testosterone, dose and type NR (33) • Gel 1%, dose NR (25) Duration: 12 mo	• Prostate cancer: 1 case in the IM group	
Guay 2000	Men with ED and primary or secondary hypogonadism	• IM TE, 200–300 mg/2–3 wk (25) • Patch, 5 mg/d (16) Duration: 2–3 mo	• Prostate cancer: 3 cases (NR which treatment group the patients belonged to)	
Prospective cohort				
Francomano 2014	Severely obese men (mean BMI 42) with ≥2 symptoms of hypogonadism	• DPE (12) • DPE + IM TU, 1000 mg/12 wk (12) Duration: 54 wk + 24 wk observational period following withdrawal of treatment	• WAE: zero in both groups • SAE: zero in both groups	
Aydogdu 2013	IHH	• Sustanon, 250 mg/3wk (28) • Gel 1%, 50 mg/d (24) Duration: 24 wk	• SAE: zero in all groups	
Blick 2013	HIV/AIDS	• Androgel 1%, gel, 50 mg/d (92) • Testim 1%, gel, 50 mg/d (75) Duration: 12 mo	• Erythrocytosis: zero in both groups • Prostate cancer: zero in both groups • WAE: zero in both groups	
Aversa 2012	Middle-aged men with LOH and MetS	• No treatment (20) • IM TU, 12 wk (40) Duration: 36 mo	• MI: 1 in control group • Erythrocytosis: 4 in TU group	
Dean 2005	21–81 yr	• Gel 1%, 50 mg/d (NR) • Gel 1%, 100 mg/d (NR)	• Prostate cancer: 3 • WAE: 40 • SAE: 6	Reported only adverse events "judged related to study medication" and that affected >1% of study population.

Study	Population	Treatment (no. in group)	Outcome	Comments
		Total: 371 men Duration: up to 12 mo		
Wang 2004	19–68 yr	• Gel 1%, 50 mg/d (NR) • Gel 1%, 75 mg/d (NR) • Gel 1%, 100 mg/d (NR) Total: 163 men Duration: 36 mo‡	•Prostate cancer: 1 in 75 mg/d group, 2 in 100 mg/d group • Skin reactions: 12 men	
Hajjar 1997	Elderly men	• No treatment (27) • IM TE or TC 200mg/2-3 wk (45) Duration: at least 2 yr	• Myocardial infarction: 1 in TRT group • Stroke: No treatment: 1/23; TRT: 1/26 • Diabetes: No treatment: 0/23; TRT: 1/26 • Erythrocytosis†: No treatment: 0/27; TRT: 11/45	Safety outcomes were reported based on a subset of people assigned to each group,

Note: BMI = body mass index, DPE = diet plus exercise, ED = erectile dysfunction, IHH = idiopathic hypogonadotropic hypogonadism, IM = intramuscular injection, LOH = late-onset hypogonadism, MetS = metabolic syndrome, MI = myocardial infarction, NR = not reported, PSA = prostate specific antigen, SAE = serious adverse event, TC = testosterone cypionate, TE = testosterone enanthate, TU = testosterone undecanoate, TRT = testosterone replacement therapy, T = testosterone, VA = Veterans Affairs, WAE = withdrawal due to adverse events.
*Composite outcome of all-cause mortality, myocardial infarction, and ischemic stroke. MI, stroke and CV death were also reported separately; however the length of observation time differed between groups.
†Reported as polycythemia for the treatment group. Zero count inferred for the control group.
‡ This study was completed after an initial 6-month randomized study for an additional 36 months; participants had a total of 42 months of gel exposure.

PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	**p. 1**
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	**p. 3**
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known*, including mention of why a network meta-analysis has been conducted.*	**p. 6**
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	**p. 6**
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	**p. 2,5,6**
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*	**p. 6-7**
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify	**p. 7**

		additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Online supplement
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	**p. 7**
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	**p. 7**
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	**p. 8**
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	**p. 8-9**
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	**p. 7-8**
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	**p. 8-9**
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	**p. 8-9**
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	**p. 8-9**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	**p. 7-8**
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses;	**NA**

		• *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	
RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	**p. 10, Figure 1**
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	**Fig 3, supplement**
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	**Supplement (eAppendix 4)**
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	**Supplement (eTable 1,2)**
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	**Supplement (eTable 3,4)**
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	**Supplement**
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	**p. 9-13, supplement**
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	**p. 10, supplement (eAppendix 5)**
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	**p. 9, Supplement (eTable 3,4)**
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, *alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	**NA**

DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	**p. 13**
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	**p. 15**
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	**p. 15-16**
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	**p. 2**

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Testosterone therapy in hypogonadal men: a systematic review and network meta-analysis

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Complete List of Authors:	Elliott, Jesse; University of Ottawa Heart Institute; University of Ottawa, School of Epidemiology and Public Health, Kelly, Shannon; Ottawa Hospital Research Institute, Cardiovascular Research Methods Centre; University of Ottawa, School of Epidemiology and Public Health Millar, Adam; Mount Sinai Hospital, University of Toronto Peterson, Joan; Clinical Epidemiology Program, Ottawa Hospital Research Institute Chen, Li; University of Ottawa Heart Institute, Cardiovascular Research Methods Centre Johnston, Amy; Cardiovascular Research Methods Centre, University of Ottawa Heart Institute Kotb, Ahmed; University of Ottawa Heart Institute, Skidmore, Becky; Independent Information Specialist Bai, Zemin; University of Ottawa Heart Institute, Cardiovascular Research Methods Centre Mamdani, Muhammad; St Michael's Hospital, Li Ka Shing Knowledge Institute Wells, George ; University of Ottawa Heart Institute, Cardiovascular Research Methods Centre; University of Ottawa, School of Epidemiology and Public Health
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Jesse Elliott, Shannon Kelly, Adam Millar, Joan Peterson, Li Chen, Amy Johnston, Ahmed Kotb, Becky Skidmore, Zemin Bai, Muhammad Mamdani, George A Wells

Jesse Elliott MSc,
Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, 40 Ruskin Street, Ottawa, Ontario, K1Y4W7

Shannon Kelly MSc,
Cardiovascular Research Methods Centre, University of Ottawa Heart Institute,
40 Ruskin Street, Ottawa, Ontario, K1Y4W7

Adam C. Millar MD MScCH
Department of Medicine, Mount Sinai Hospital, University of Toronto, Toronto, Ontario

Joan Peterson BSc,
Clinical Epidemiology Program, Ottawa Hospital Research Institute, 1053 Carling Avenue, Ottawa, Ontario, K1Y 4E9

Li Chen MSc,
Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, 40 Ruskin Street, Ottawa, Ontario, K1Y4W7

Amy Johnston MSc,
Cardiovascular Research Methods Centre, University of Ottawa Heart Institute,
40 Ruskin Street, Ottawa, Ontario K1Y4W7

Ahmed Kotb MSc,
Royal College of Surgeons in Ireland, 123 St. Stephen's Green, Dublin, Ireland

Becky Skidmore MLS,
Independent Information Specialist, Ottawa, Ontario, K1T 3Z2

Zemin Bai MSc,
Cardiovascular Research Methods Centre, University of Ottawa Heart Institute,
40 Ruskin Street, Ottawa, Ontario K1Y4W7

Muhammad Mamdani PharmD,
Li Ka Shing Knowledge Institute, St. Michael's Hospital; Toronto, Ontario M5B1W8

George A. Wells PhD, Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, 40 Ruskin Street, Ottawa, Ontario, K1Y4W7

Correspondence to: GA Wells, gawells@ottawaheart.ca

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Registration: PROSPERO number: CRD42014009963

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Contributors: JE, SK, MM, and GW designed the study. BS developed and executed the search strategy. JE, SK, JP, AJ, AK, and ZB selected studies for inclusion and extracted data. JE, AK, and LC analyzed the data. JE, SK, LC, AM, and GW interpreted the data. JE wrote the first draft of the manuscript, which

was critically revised for intellectual content by all authors. All authors approved the final version submitted for publication and agree to be accountable for all aspects of the study.

Keywords: testosterone, benefits, depression, quality of life, erectile function, libido, harms, cardiovascular-related adverse events, systematic review, network meta-analysis

ABSTRACT

Objective: To assess the relative effects of individual testosterone products among hypogonadal men.

Design: Systematic review and network meta-analysis.

Methods: We searched MEDLINE, Embase, Cochrane CENTRAL, and grey literature (May 25, 2017) for randomized controlled trials (RCTs) and non-randomized studies (NRS) that involved hypogonadal men given testosterone replacement therapy (TRT) for ≥ 3 months. Comparators were placebo, another TRT, or the same product at a different dose. Outcomes were quality of life, depression, libido, erectile function, activities of daily living, and testosterone levels, as well as cardiovascular death, myocardial infarction, stroke, prostate cancer, heart disease, diabetes, serious adverse events, withdrawals due to adverse events, and erythrocytosis. RCT data were pooled via meta-analysis and network meta-analysis. Risk of bias was assessed using Cochrane's Risk of Bias tool (RCTs) and SIGN50 (NRS).

Results: 87 RCTs and 51 NRS were included. Most were at high or unclear risk of bias, with short treatment duration and follow-up. When compared as a class against placebo, TRT improved quality of life (standardized mean difference [SMD] -0.26, 95% confidence interval [CI] -0.41,-0.11), libido (SMD 0.33, 95%CI 0.16,0.50), depression (SMD -0.23, 95%CI -0.44,-0.01), and erectile function (SMD 0.25, 95%CI 0.10,0.41). Most individual TRTs were significantly better than placebo at improving libido (6/10). Only one TRT was better than placebo at improving quality of life, and no individual TRTs improved depression or erectile function. There was no increased risk of adverse events, with the exception of withdrawals due to adverse events with the use of some TRTs.

Conclusion: Despite a class effect of improving quality of life, depression, erectile function, and libido, major improvements were not observed with the use of any individual product. We observed no statistically significant increase in the risk of adverse events; however, longer-term high-quality trials are needed to fully assess the risk of harm.

Registration: PROSPERO CRD42014009963

Article Summary

Strengths and limitations

• We performed a comprehensive systematic review of the published and grey literature to identify randomized and non-randomized studies involving adult men with low testosterone levels

• Although there is no universally agreed on level for the diagnosis of "low" testosterone, we included only studies that enrolled men with total testosterone ≤ 12 nmol/L or free testosterone ≤ 225 pmol/L, consistent with recent guidelines.

• Data from non-randomized studies were poorly reported and were not suitable to pooling via meta-analysis.

• The included studies were generally at high or unclear risk of bias, and most studies had a relatively short treatment duration.

• Long-term high-quality studies are needed to more fully assess the risk of rare adverse events.

Introduction

Testosterone deficiency has well-recognized negative effects on male sexuality and quality of life.[1] Recent clinical practice guidelines recommend testosterone replacement therapy (TRT) for adult men with low testosterone levels (hypogonadal men) with the goal of improving symptoms and elevating testosterone levels into the mid-normal range for young men.[2] However, two large observational studies have reported an increased risk of cardiovascular events with testosterone use,[3,4] and the US Food and Drug Administration (FDA) and Health Canada both have warned of a potential increased risk of cardiovascular events among men using testosterone products.[5,6]

Previous meta-analyses have reported positive effects of TRT compared with placebo, on quality of life,[7] depression,[8,9] and some aspects of sexual function.[10] However, the results of individual trials have been mixed, and there is variation in testosterone formulations and doses.[11] Similarly, previous meta-analyses of potential harms related to TRT have reported contradictory findings.[12–16] A 2013 meta-analysis reported an increased risk of cardiovascular-related events in a mixed population of hypogonadal and eugonadal men[15]; however, others have found no increased risk of cardiovascular outcomes, including myocardial infarction, stroke, or cardiovascular death.[12–14,16]

Because each TRT product has a different formulation and many different dosing strategies exist,[17] it may not be appropriate to group together all testosterone products, as in traditional meta-analyses. In this study, we performed a systematic review to identify randomized controlled trials (RCTs) and non-randomized studies (NRS) involving hypogonadal men, and we used network meta-analysis to compare the relative benefits and harms of each product.

Methods

This review was registered *a priori* (CRD42014009963) and followed the Cochrane handbook[18] and the PRISMA for Network Meta-Analysis checklist.[19] Our review included RCTs and NRS involving adult

men with low testosterone taking any form of TRT compared to placebo, another TRT, or the same product at a different dose. We did not exclude studies on the basis of reported outcomes.

Patient involvement: No patients were involved in setting the research question or in developing plans for design, or implementation of the study. A patient representative was involved in selecting the outcome measures, and patient groups were given the opportunity to comment on the study protocol. No patients were asked to advise on the interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Search strategy: Using the OVID platform, we searched Ovid MEDLINE, Ovid MEDLINE In-Process & Other Non-Indexed Citations, and Embase Classic+Embase on June 3, 2014. We also searched CENTRAL in the Cochrane Library on Wiley on the same date. grey literature were searched according to CADTH's Grey Matters Light.[20] All searches were updated on May 25, 2017.

We used controlled vocabulary, including "Testosterone", "Testosterone Congeners" and "Androgens", to which we applied relevant subheadings "administration & dosage", "analogs & derivatives", "adverse events" and "therapeutic use", or combined with "Hormone Replacement Therapy." Our keywords included "testosterone" or "androgen" in combination with means of administration (buccal, cream, gel, implant, injections, oral, patch, transdermal) or function (replacement, substitute, supplement, therapy, treatment). We also searched "TRT" and all known names for testosterone replacement products (e.g., androgel, Bio-T-Gel, Striant). Truncation, wildcards and proximity operators were incorporated as appropriate and terminology and syntax were adjusted according to database and platform. The search strategy is available in eAppendix1.

Study selection: We included placebo- and active-controlled RCTs and NRS involving adult men (≥ 18 yr) with low testosterone (total testosterone ≤ 12 nmol/L or free testosterone < 225 pmol/L) administered a testosterone product. We excluded studies that artificially suppressed endogenous testosterone, involved testosterone precursors, or had less than 10 participants. We included studies with a treatment duration of

12 weeks or longer, as follow-up is generally recommended for this time point.[2,21] Cross-over trials were included if the initial period was at least 12 weeks. Titles and abstracts were screened in duplicate (JE, JP), and the full-text of any potentially relevant record was evaluated (JE, JP, AJ, ZB). Disagreements were resolved by consensus.

Data extraction and risk of bias: Data were extracted by one reviewer using piloted standardized abstraction forms (Distiller SR) and checked by a second reviewer (JE, JP, AJ, AK, ZB). First-period data were extracted from cross-over trials. Risk of bias was assessed by two reviewers using the Cochrane Collaboration's risk of bias tool for RCTs or SIGN50 for cohort studies.[22] Disagreements were resolved by discussion. Publication bias was assessed by visual inspection of funnel plots.

Outcomes: Outcomes of interest were quality of life, depression, libido, erectile function, activities of daily living, and total testosterone level (at 3 mo, 6 mo, end of study) (continuous outcomes), as well as cardiovascular death, myocardial infarction, stroke, prostate cancer, diabetes, heart disease, serious adverse events, withdrawals due to adverse events, and erythrocytosis (dichotomous outcomes). We included data for quality of life, depression, erectile function, and libido that had been measured using a validated scale (eAppendix2), and the direction of each scale was standardized before analysis. A higher effect estimate (e.g., positive SMD or MD) indicates improvement in libido, erectile function and testosterone level, and a lower effect estimate indicates improvement in quality of life and depression. Data from RCTs were included for quality of life, depression, libido, erectile function, and activities of daily living, and testosterone levels, and data from RCTs and NRS were included for harms outcomes.

Data analysis*:* The results of the included NRS are summarized narratively. Meta-analysis and network meta-analysis involving data from RCTs were performed as described below. We performed meta-analysis using RevMan (v.5.3; Cochrane Collaboration) and Bayesian network meta-analysis using WinBUGS (v.1.4.3; MRC Biostatistics Unit). Analyses were based on mean change from baseline for quality of life, depression, erectile function, libido, and on mean after-treatment values for total

testosterone level. The number randomized was used as the denominator for quality of life, depression, libido, erectile function, and total testosterone level, and the number who received treatment was used for harms. Two trials[23,24] were removed from the analyses because the data from these trials were outliers for each outcome and each had a considerable effect on heterogeneity. In an exploratory analysis, we removed trials enrolling men with major comorbidities (i.e., HIV/AIDS, osteoporosis, metabolic syndrome, type 2 diabetes, angina, Alzheimer's disease, heart failure, end-stage renal disease).

In the network meta-analysis, we used a binomial likelihood model for dichotomous outcomes and a normal likelihood model for continuous outcomes, allowing for the inclusion of multi-arm trials.[25] Network meta-analyses included all trials that reported each outcome with no restrictions based on comorbidities. Each dose of an individual testosterone product was included as a separate node in the evidence networks. A continuity correction was applied to adjust zero events for harm outcomes. Assessment of model fit and choice of model (fixed v. random effects) was based on assessment of the deviance information criterion and comparison of residual deviance to the number of unconstrained data points.[25] Results are reported for the random-effects model. We derived point estimates and 95% credible intervals (CrIs) using the Markov Chain Monte Carlo method. Mean differences (MDs), standardized mean differences (SMDs) with standard deviations (SDs) or odds ratios (ORs) with 95% CrIs or CIs are reported for continuous or dichotomous outcomes as appropriate. Vague priors (e.g., $N[0, 100^2]$) were assigned for basic parameters throughout.[25] To ensure model convergence, trace plots and Brooks-Gelman-Rubin statistics were assessed.[26] Three chains were fit for each analysis with at least 20,000 iterations and a burn-in of at least 20,000 iterations. Inconsistency was assessed where possible by comparing the deviance, between-study variance, and deviance information criterion statistics of the consistency and inconsistency models.[27] The posterior mean deviance of the individual data points in the inconsistency model was plotted against the posterior mean deviance in the consistency model.[27] All network diagrams were constructed using NodeXL.

Role of the funding source: The funder had no role in study design, data collection, analysis, interpretation, or writing. All authors had full access to the study data, and the corresponding author had final responsibility for the decision to submit for publication.

Results

Search results and study characteristics

We identified 87 RCTs and 51 NRS published between 1997 and 2017, corresponding to 196 records (Figure 1, eAppendix 3). Of these, 70 RCTs and 19 NRS reported an outcome of interest (eTable1,2). The median treatment duration of the RCTs was 6 months (range: 3–36 mo), with mean participant age ranging between 30 and 78 years (eAppendix 4, eTable1). Most RCTs were placebo controlled (87%), with 2 treatment groups (89%). Of the included NRS, 10 were retrospective and 9 were prospective cohorts, with a duration up to 8 years (eTable2). Few RCTs or NRS were at low risk of bias, primarily because of a lack of details about randomization procedures, allocation concealment, and analysis populations (eTable3,4). Based on visual inspection of funnel plots, publication bias could not be ruled out for most outcomes (eAppendix 5).

Network consistency

Comparison of the consistency and inconsistency models for libido and total testosterone levels did not show evidence of inconsistency (eAppendix6). Consistency could not be evaluated for quality of life, depression, or erectile function because of a lack of closed loops. The full network characteristics and evidence networks are presented in eAppendix7.

Outcomes

Quality of life: In total, 23 RCTs (21 placebo-controlled, 2 active-controlled) involving 3090 participants assessed quality of life. Compared with placebo, treatment with any TRT significantly improved quality of life (SMD –0.26, 95%CI –0.41,–0.11; n = 2834) with substantial heterogeneity (I^2 = 71%; Figure 2A).

To explore this heterogeneity, we excluded RCTs that involved men with major comorbidities. This had little effect on heterogeneity (I^2 = 62%) or the point estimate (SMD –0.17, 95%CI –0.34,–0.01; Figure 2B).

The evidence network for quality of life comprised 23 RCTs, representing 14 treatments in addition to placebo (Figure 3). Intramuscular (IM) testosterone undecanoate (TU; 1000 mg/12 wk) significantly improved quality of life relative to placebo (SMD -0.48, 95%CI -0.84, -0.10) and to oral TU (160 mg/d; SMD -0.68, 95%CI -1.32, -0.02), with no other significant differences among the other treatments (Table 1). The results were consistent when studies involving men with major comorbidities were removed from the network, despite 3 fewer treatments being included in the network (data not shown).

Depression: Twelve RCTs (11 placebo-controlled, 1 active controlled) involving 852 participants randomized to 9 treatments evaluated depression. Compared with placebo, treatment with any TRT had improved depression (SMD –0.23, 95%CI –0.44,-0.01; n = 786;I^2 = 44%) (eAppendix 8 [eFigure2A]). Removal of trials involving men with major comorbidities did not reduce heterogeneity, and the effect of TRT was no longer statistically significant (SMD –0.12, 95%CI –0.49,0.26; I^2 = 56%) (eFigure2B).

In the network meta-analysis, there were no significant differences in depression for any individual TRT compared with placebo or among the treatments (eTable5). Removal of trials involving major comorbidities did not alter the results (2 treatments removed; data not shown).

Libido: Fourteen RCTs (12 placebo-controlled, 2 active-controlled) involving 3167 patients randomized to 10 treatments investigated libido. Compared with placebo, treatment with any TRT significantly improved libido (SMD 0.33, 95%CI 0.16,0.50; I^2 = 74%; n = 2732) (eFigure3A). Removal of trials involving men with major comorbidities increased heterogeneity (I^2 = 80%), and the point estimate was no longer statistically significant (SMD 0.19, 95%CI –0.03,0.41) (eFigure3B).

In the network meta-analysis, most individual treatments significantly improved libido compared with placebo (6/10 treatments; eTable6). Among the treatments, 1% gel (100 mg/d) was significantly better than patch (5 mg/d) and oral TU (160 mg/d), and oral TU (120 mg/d) was significantly better than patch (5 mg/d) and 1% gel (75 mg/d). Oral TU (160 mg/d) was significantly worse than most other TRTs in the network (8/9 TRTs) (eTable6). Removal of trials involving major comorbidities resulted in the removal of 4 treatments from the network; however, the results were consistent for the remaining treatments (data not shown).

Erectile function: 17 RCTs (all placebo-controlled) involving 3165 patients randomized to 9 treatments evaluated erectile function. Compared with placebo, treatment with any TRT improved erectile function (SMD 0.25, 95%CI 0.10, 0.41), with substantial heterogeneity (I^2 = 74%; eFigure4A). Removing trials involving men with major comorbidities reduced heterogeneity (I^2 = 58%), with no qualitative change to the point estimate (SMD 0.36, 95%CI 0.21, 0.51; eFigure4B).

In the network meta-analysis, there were no significant differences in erectile function between placebo and any individual TRT or among the treatments (eTable7). Removal of trials involving major comorbidities did not alter the results (2 treatments removed; data not shown).

Activities of daily living: One RCT reported no significant difference in activities of daily living among men with mild cognitive impairment following 6 months of TRT (testosterone gel 50–100 mg/d) compared with placebo (p = 0.31).[28]

Testosterone levels: In total, 26 and 23 RCTs reported total testosterone levels after 3 or 6 months of treatment, respectively. End of treatment testosterone levels were reported in 57 RCTs. After 3 or 6 months of treatment, about half of the treatments in each network were associated with significantly higher total testosterone levels compared with placebo (3 mo: 6/15; 6 mo: 11/18) (eTables 8,9). By the end of treatment (12 wk to 36 mo), most products were associated with total testosterone above 12

nmol/L (26/28 testosterone therapies), and 17 of 28 treatments had significantly higher levels relative to placebo (eTable10).

Cardiovascular death: 10 RCTs reported the occurrence of cardiovascular death during the treatment period, while an additional 9 trials reported that no CV deaths had occurred (18 placebo-controlled RCTs). Compared with placebo via pair wise meta-analysis, there was no significant difference in the risk of cardiovascular death between placebo and any TRT (all products grouped together) (OR 2.15, 95% CI 0.72,6.45; I^2 = 11%) (Figure 4; Table 2). Because of the low event rate, network meta-analysis did not provide robust estimates for this outcome (data not reported).

Other adverse events: Compared with placebo via meta-analysis, there were no increased odds of myocardial infarction, stroke, prostate cancer, heart disease, or erythrocytosis with the use of any TRT product (Table 2; eFigure 6-11). Withdrawals due to adverse events were significantly greater with the use of any TRT compared with placebo (OR 1.31, 95% CI 0.95, 1.73; I^2 = 13%)(eFigure12). No RCTs reported incident diabetes during the treatment period.

Owing to the low event rates for most outcomes, network meta-analysis was only possible for serious adverse events and withdrawals due to adverse events. In the head-to-head comparison of TRTs, there was no significant difference in serious adverse events between any TRT and placebo or among the TRTs (eTable11). Use of testosterone patch (5 mg/d) was associated with an increased odds of withdrawal compared with placebo and many of the other TRTs (eTable12).

Nonrandomized studies

The reporting of harms in the included NRS was generally poor, primarily because of a lack of transparency around the number of patients assigned to each group, the number of events per group, and/or the type or dose of TRT (eTable13). In the longest prospective cohort study, involving 656 men followed for up to 10 years,[29] men who had received IM TU (1000 mg/12 wk) were at lower risk of death

(incidence of death: TRT group 0.0092 [95%CI 0.0032,0.0368]; no TRT group 0.1145 [95%CI 0.0746, 0.1756]), with 19 of 21 deaths in the control group attributed to cardiovascular causes and zero of 2 deaths in the TRT group due to cardiovascular causes. Non-fatal MI and non-fatal stroke were also more common in the untreated group than in the TRT group (TRT group: 0 MI, 0 stroke; no TRT group: 26 MI, 30 stroke). In a large retrospective cohort study in the US involving 8808 men dispensed a TRT product and 35,527 men never dispensed TRT,[30] men in the TRT group were at lower risk of sudden cardiovascular death (adjusted hazard ratio [aHR] 0.76, 95%CI 0.61, 0.93), acute MI (aHR 0.74; 95%CI 0.63, 0.86), and stroke (aHR 0.64, 95% CI 0.52, 0.80) over a median follow-up time of 3.4 years. In contrast, an earlier retrospective cohort study involving among men who had undergone angiography reported that those who had filled a prescription for TRT were at higher risk of an adverse cardiovascular event (aHR 1.29, 95%CI 1.05,1.15) compared men with no TRT prescription.[3] Concerning the relative safety of the different TRTs, one retrospective cohort study[31] reported no significant difference in risk between injection or gel TRT users with low testosterone at baseline for MI (aHR1.64, 95%CI 0.57, 4.69) stroke (aHR 1.28, 0.27, 6.02), or death (a HR 5.53, 95% CI 0.98, 31.15).

Prostate cancer was reported by 10NRS.[29,32–40],[41] In a large prospective registry (Registry of Hypogonadism in Men) involving 999 newly diagnosed hypogonadal men,[37] there was no statistically significant difference in the risk of prostate cancer between men who used or did not use TRT (incidence rate ratio 0.52, 95%CI 0.22, 1.26). Traish and colleagues[29] also reported fewer cases of prostate cancer among men who received TRT (IM TU) compared with hypogonadal men who did not receive TRT (TU: 7/360 men v. no TRT: 12/296 men) over a median follow-up of 7 years, and Yassin and colleagues[35] reported positive biopsies for prostate cancer among 16.7% of TRT users compared with 51.9% of non-users, as well as a lower severity in terms of staging and grading in their prospective study of prostate cancer among hypogonadal men. Among men with a previous diagnosis of prostate cancer, one small retrospective cohort study[41] reported no recurrences of prostate cancer among TRT users during the follow-up period (2630 months). The reporting of outcomes and treatment group in most of the remaining

studies was poor: either the group assignment of the men who experienced prostate cancer or the number of men in each treatment group was not reported in each (eTable13).[38,33,34]

DISCUSSION

Despite more than 70 years of clinical use, TRT remains a controversial topic. Part of the controversy may be a result of different actions of the various testosterone preparations. In an attempt to clarify the benefits and harms of individual testosterone products, we used traditional pair-wise meta-analysis as well as network meta-analysis, which allows the relative comparison of products that have not been compared in head-to-head trials. Consistent with most previous meta-analyses,[8],[7,10] we found that the use of TRT improved quality of life, depression, libido, and erectile function, with no increase in cardiovascular death or other major adverse events.

In the head-to-head comparison of individual testosterone treatments, we found no significant differences among products in their effect on depression or erectile function. For libido, testosterone gel (1%, 100 mg/d) was significantly better than testosterone patch (5 mg/d) and oral TU (160 mg/d). Oral TU (160 mg/d) was significantly worse than most other treatments in the network, including oral testosterone undecanoate at 120 mg/d. The finding that a lower dose of oral TU was more effective than a higher dose was unexpected and requires further investigation.

Conflicting data exist about the risk of adverse cardiovascular events among TRT users. The FDA and Health Canada both issued alerts in 2015 based in part on the findings of two observational studies.[3,4] In their retrospective cohort, Vigen and colleagues[3] included men with low testosterone who had undergone angiography, reporting an increased risk of a composite cardiovascular outcome that included all-cause mortality, myocardial infarction, and stroke (aHR 1.29, 95%CI 1.04, 1.58). Most participants in this study were receiving TRT in the form of a patch (63%) and had significant medical comorbidities, which may limit generalizability. The retrospective study by Finkle and colleagues[4] did not report the baseline testosterone level of men in their cohort nor was the cohort restricted to men with androgen deficiency; as

such, this study was not eligible for inclusion in our review, but their findings that the risk of non-fatal MI is increased in the first 90 days following testosterone prescription is concerning. However, other recent large observational studies have reported a lower risk of cardiovascular death, stroke and MI among TRT users,[29,30] supporting the findings of earlier observational studies that reported a lower risk of all-cause death among hypogonadal men using TRT. [40]

Previous meta-analyses have also reported contradictory findings concerning the risk of adverse events among TRT users. One meta-analysis reported an increase risk of cardiovascular adverse events among men using TRT,[15] while a number of other meta-analyses have found no increased risk of cardiovascular events among TRT users.[12–14,16,42,43] The meta-analysis by Xu and colleagues[15] involved a broad composite outcome (cardiac disorder, cardiovascular complaints, cardiovascular events, vascular disorders) and has been criticized for use of a fixed-effects model: subsequent reanalysis using a random-effects model found no significant increase in the risk of cardiovascular events.[43] Our findings are consistent with previous meta-analyses that have found no increased risk of individual cardiovascular events compared with placebo.[12–14,16,43,42]

Although we had intended to analyze the effects of individual testosterone products among men aged 65 years and older, data were limited because most RCTs included a wide age range. The Testosterone Trials were designed to address the lack of data among elderly men.[44] After one year of treatment with 1% testosterone gel, improved desire and erectile function were reported among men with low sexual function at baseline, with no apparent increase in the risk of adverse cardiovascular events.[44] Although these findings are encouraging, the trials were not powered to detect adverse events, and the results should not be generalized to different testosterone preparations.

Strengths and limitations

The strengths of this study include a comprehensive search of the published and grey literature without language or date restrictions. In contrast with previous reviews, we included only studies that enrolled men with total testosterone ≤ 12 nmol/L or free testosterone ≤ 225 pmol/L. Although there is no universally agreed on threshold value for low testosterone, a recent guideline recommends TRT for men with total testosterone lower than 12 nmol/L.[11]

Our study had several limitations. First, the included studies used a variety of assays to determine testosterone levels and a variety of cut-off values for determining "low" testosterone. This has been noted by others.[11,45] The US Centers for Disease Control and Prevention's Hormone Standardization Project[46] will help to resolve this issue. Second, the included RCTs and NRS were generally at unclear or high risk of bias, which may have had an impact on the reliability of subjective data. Third, the duration of treatment and the length of follow-up may have been too short to see an effect of TRT for all outcomes, including adverse events. In keeping with the recommendation to reassess symptoms after 3 months of TRT,[21] we included only studies with a treatment duration of 3 months or longer. The median duration of treatment was 6 months in the RCTs, but it is possible that some symptoms may take longer to resolve.

Conclusions

To the best of our knowledge, this is the first study to compare the benefits and harms of individual testosterone products among hypogonadal men. Our study builds on previous meta-analyses by comparing the relative effects of individual testosterone treatments, most of which have never been compared in head-to-head trials. When considered as a class (any TRT compared to placebo), TRT improved quality of life, depression, erectile function, and libido; however, when the individual products were compared head to head, there were few differences between the treatments. We found no increased risk of major harms; however, this must be viewed in light of the high risk of bias of the included studies, the rare nature of serious harms, and the short treatment duration and follow-up of most studies. Future

studies need to be rigorous in design and delivery, and include comprehensive descriptions of all aspects of methodology to further enable appraisal and interpretation of results.

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Figure legends

Figure 1: PRISMA flow diagram showing selection of studies.

Figure 2: Meta-analysis of the effect of testosterone on quality of life. (A) All randomized controlled trials (RCTs), and (B) RCTs involving men with no major comorbidities.

Figure 3: Evidence network for quality of life. The size of each circle (node) is proportional to the number of randomly assigned patients and indicates sample size. The number of randomized controlled trials that contributed to each direct comparison is indicated on each line. IM = intramuscular injection, TC = testosterone cypionate, TE = testosterone enanthate, TU = testosterone undecanoate.

Figure 4: Odds of cardiovascular death associated with the use of any testosterone product v. placebo

Tables

Table 1: Quality of life – Indirect comparison of testosterone products*

	Standardized mean difference (95% confidence interval)														
	Placebo	**Patch, 5 mg/d**	**Gel 1%, 5 mg/d**	**Gel 1%, 50 mg/d**	**Gel 1%, 75 mg/d**	**Gel 1%, 100 mg/d**	**Gel 2%, 60 mg/d**	**Oral TU, 160 mg/d**	**IM TU, 1000 mg/ 10 wk**	**IM TU, 1000 mg/ 12 wk**	**IM TE, 250 mg/ 3 wk**	**IM TE, 250 mg/ 4 wk**	**IM TC, 200 mg/ 4 wk**	**IM Sustanon, 100 mg/2 wk**	**IM Durateston, 250 mg/4 wk**
Patch, 5 mg/d	-0.33 (-0.97, 0.31)	—													
Gel 1%, 5 mg/d	-0.11 (-0.86, 0.64)	0.21 (-0.78,1.20)	—												
Gel 1%, 50 mg/d	-0.32 (-0.74, 0.17)	0.01 (-0.76,0.82)	-0.20 (-1.05,0.69)	—											
Gel 1%, 75 mg/d	-0.24 (-0.83, 0.34)	0.09 (-0.78,0.95)	-0.12 (-1.09,0.82)	0.08 (-0.70,0.79)	—										
Gel 1%, 100 mg/d	-0.19 (-0.94, 0.55)	0.13 (-0.84,1.10)	-0.08 (-1.13,0.97)	0.12 (-0.78,0.96)	0.04 (-0.89,0.99)	—									
Gel 2%, 60 mg/d	-0.29 (-1.01,0.44)	0.04 (-0.93,1.00)	-0.17 (-1.21,0.87)	0.03 (-0.85,0.86)	-0.05 (-0.96,0.89)	-0.09 (-1.12,0.94)	—								
Oral TU, 160 mg/d	0.20 (-0.33,0.74)	0.53 (-0.30,1.36)	0.32 (-0.61,1.24)	0.52 (-0.21,1.19)	0.44 (-0.34,1.24)	0.40 (-0.51,1.31)	0.49 (-0.41,1.38)	—							
IM TU, 1000 mg/10 wk	-0.21 (-0.96, 0.56)	0.12 (-0.87,1.13)	-0.09 (-1.15,0.98)	0.11 (-0.80,0.98)	0.03 (-0.92,1.00)	-0.01 (-1.07,1.06)	0.08 (-0.97,1.14)	-0.41 (-1.35,0.53)	—						
IM TU, 1000 mg/12 wk	**-0.48 (-0.84,-0.10)**	-0.15 (-0.89,0.60)	-0.36 (-1.19,0.48)	-0.16 (-0.76,0.41)	-0.24 (-0.91,0.47)	-0.28 (-1.10,0.55)	-0.19 (-1.00,0.62)	**-0.68 (-1.32,-0.02)**	-0.27 (-1.12,0.58)	—					
IM TE, 250 mg/3 wk	-0.05 (-1.04,0.94)	0.28 (-0.47,1.03)	0.07 (-1.17,1.30)	0.27 (-0.85,1.33)	0.19 (-0.95,1.34)	0.15 (-1.09,1.37)	0.24 (-1.00,1.46)	-0.25 (-1.38,0.88)	0.16 (-1.10,1.40)	0.43 (-0.63,1.49)	—				
IM TE, 250 mg/4 wk	0.08 (-0.44,0.63)	0.41 (-0.41,1.26)	0.20 (-0.72,1.13)	0.40 (-0.32,1.09)	0.32 (-0.44,1.13)	0.28 (-0.62,1.21)	0.37 (-0.51,1.28)	-0.12 (-0.86,0.66)	0.29 (-0.64,1.22)	0.56 (-0.09,1.22)	0.13 (-0.97,1.27)	—			
IM TC, 200 mg/4 wk	0.12 (-1.00,1.25)	0.45 (-0.83,1.74)	0.24 (-1.10,1.59)	0.44 (-0.78,1.64)	0.36 (-0.89,1.63)	0.32 (-1.03,1.66)	0.41 (-0.92,1.74)	-0.08 (-1.32,1.18)	0.33 (-1.01,1.68)	0.60 (-0.46,1.67)	0.17 (-1.32,1.66)	0.04 (-1.20,1.28)	—		
IM Sustanon, 100 mg/2 wk	-0.28 (-1.17,0.62)	0.05 (-1.05,1.14)	-0.16 (-1.32,1.01)	0.04 (-0.99,1.02)	-0.04 (-1.10,1.03)	-0.08 (-1.24,1.09)	0.01 (-1.13,1.16)	-0.48 (-1.52,0.57)	-0.07 (-1.24,1.11)	0.20 (-0.77,1.16)	-0.23 (-1.56,1.11)	-0.36 (-1.42,0.67)	-0.40 (-1.84,1.02)	—	
IM Durateston 250 mg/4wk	-0.37 (-1.49,0.74)	-0.05 (-1.33,1.24)	-0.26 (-1.61,1.09)	-0.06 (-1.27,1.12)	-0.14 (-1.37,1.13)	-0.18 (-1.51,1.16)	-0.08 (-1.40,1.23)	-0.57 (-1.81,0.66)	-0.17 (-1.52,1.17)	0.10 (-0.95,1.15)	-0.33 (-1.81,1.17)	-0.46 (-1.70,0.76)	-0.50 (-1.52,0.52)	-0.10 (-1.52,1.33)	—

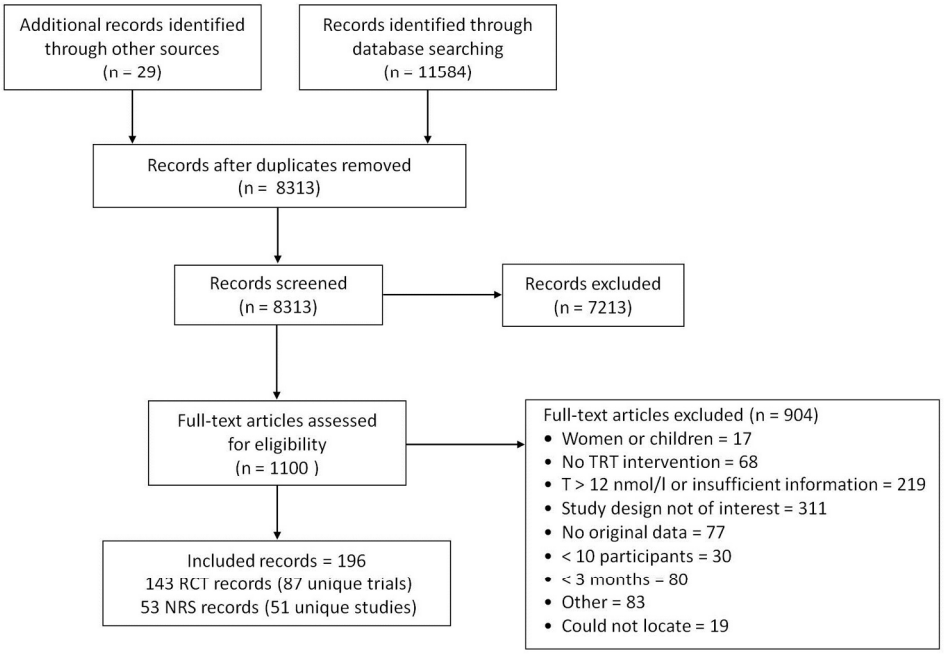
Note: IM = intramuscular injection, TC = testosterone cypionate, TE = testosterone enanthate, TU = testosterone undecanoate.

*Random-effects model, with analysis based on mean change from baseline. A negative standardized mean difference indicates improvement in quality of life. Statistically significant changes are indicated by use of bold and colour (green indicates that the row treatment is significantly better than the column treatment, red indicates that the row treatment is significantly worse than the column treatment). White indicates no significant difference between treatments.

Table 2: Meta-analysis of adverse events associated with the use of any testosterone compared with placebo

Outcome	No. of RCTs	Treatment duration	Event/no. treated	Odds ratio (95% CI)*	I^2
Cardiovascular death	18	12 wk to 36 mo	Placebo: 4/1851 TRT: 9/2088	2.15 (0.72, 6.45)	11%
Myocardial infarction	15	12 wk to 36 mo	Placebo: 10/1613 TRT: 6/1915	0.43 (0.15, 1.19)	34%
Prostate cancer	13	12 wk to 36 mo	Placebo: 11/1649 TRT: 12/1877	0.97 (0.43, 2.23)	0%
Stroke	8	12 wk to 36 mo	Placebo: 8/1103 TRT: 8/1104	0.99 (0.37, 2.65)	29%
Heart disease	3	40 wk to 12 mo	Placebo: 5/120 TRT: 5/131	0.89 (0.24 to 3.26)	0%
Erythrocytosis	4	12 wk to 12 mo	Placebo: 0/78 TRT: 4/110	2.44 (0.26, 22.53)	0%
Diabetes	0	—	—	—	—
Serious adverse events	18	12 wk to 36 mo	Placebo: 181/1902 TRT: 168/2138	0.88 (0.70, 1.11)	0%
Withdrawals due to adverse events	48	12 wk to 36 mo	Placebo: 150/2551 TRT: 221/2840	1.31 (0.98, 1.73)	13%

Note: CI = confidence interval, TRT = testosterone replacement therapy.
*Random-effects models.



PRISMA flow diagram showing selection of studies.

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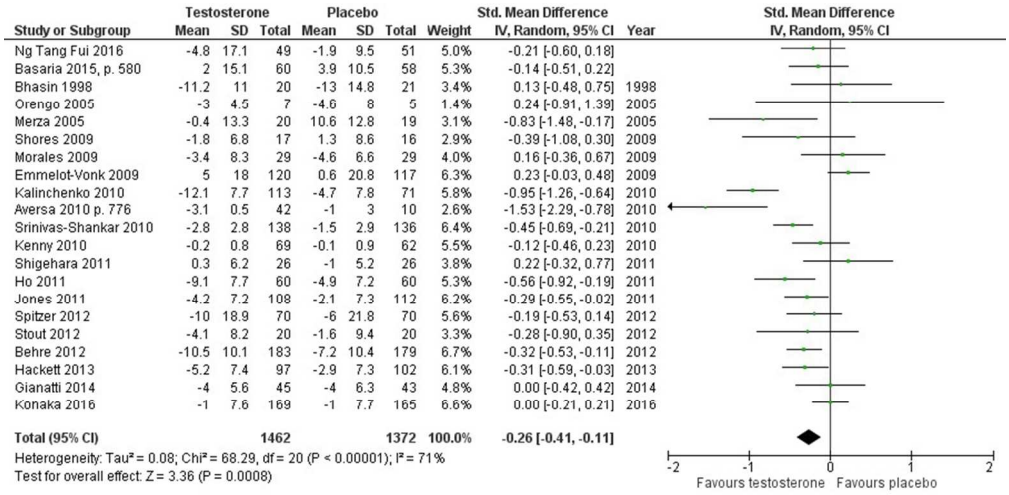
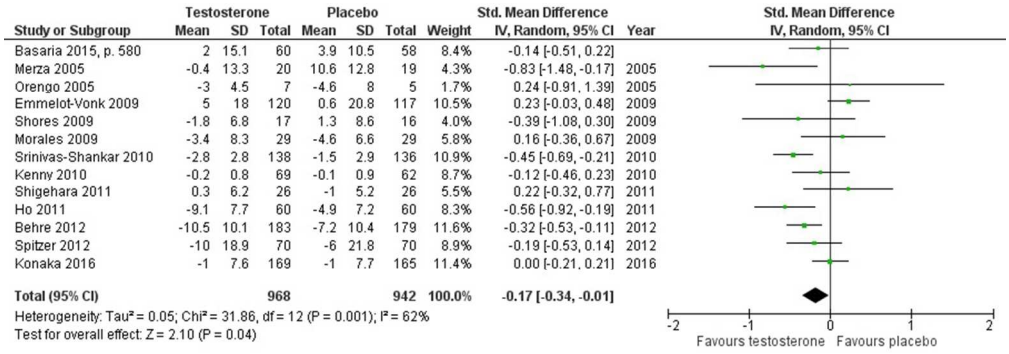


Meta-analysis of the effect of testosterone on quality of life. (A) All randomized controlled trials (RCTs), and (B) RCTs involving men with no major comorbidities.

76x37mm (300 x 300 DPI)



Meta-analysis of the effect of testosterone on quality of life. (A) All randomized controlled trials (RCTs), and (B) RCTs involving men with no major comorbidities.

76x27mm (300 x 300 DPI)

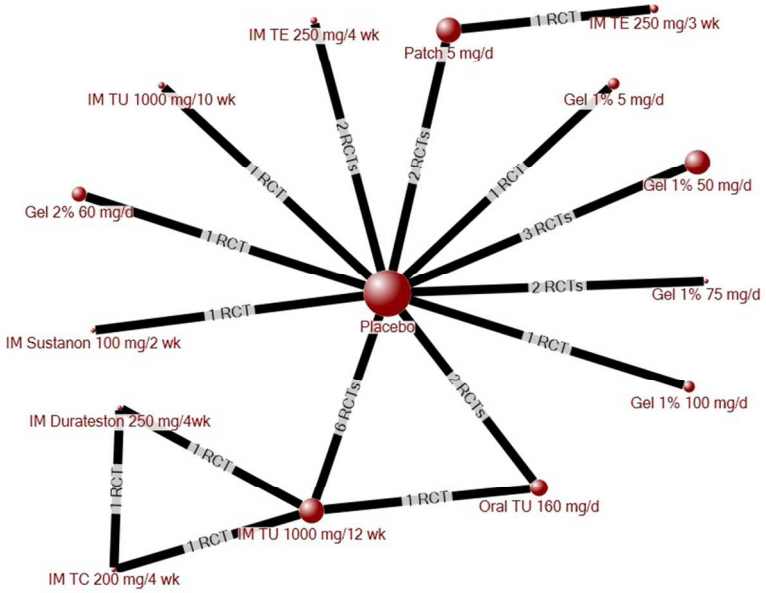
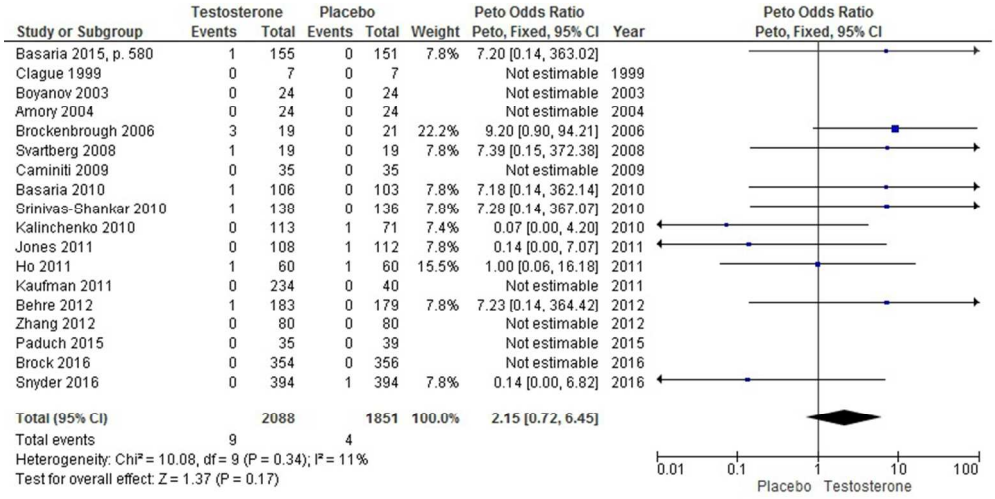


Figure 3: Evidence network for quality of life. The size of each circle (node) is proportional to the number of randomly assigned patients and indicates sample size. The number of randomized controlled trials that contributed to each direct comparison is indicated on each line. IM = intramuscular injection, TC = testosterone cypionate, TE = testosterone enanthate, TU = testosterone undecanoate.

89x57mm (300 x 300 DPI)



Odds of cardiovascular death associated with the use of any testosterone product v. placebo

70x35mm (300 x 300 DPI)

Supplementary Online Content:

Elliott et al. Testosterone replacement therapies in hypogonadal men: a systematic review and network meta-analysis

eAppendix 1: Search strategy

The search was originally executed on June 3, 2014 and updated May 25, 2017.

Testosterone Replacement Therapy
Primary Studies - Final Strategies
2014 Jun 3

Database: Embase Classic+Embase <1947 to 2014 June 02>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present> Search Strategy:

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1 exp Testosterone/aa, ad, ae, tu (9143)
2 Testosterone Congeners/ad, ae, tu (391)
3 exp Testosterone/ and Hormone Replacement Therapy/ (4361)
4 exp Androgens/ and Hormone Replacement Therapy/ (5792)
5 (testosteron* adj3 (replac* or substitut* or supplement* or therap* or treatment* or buccal or cream$1 or gel or gels or implant* or inject* or oral* or patch* or transdermal*)).tw. (20369)
6 (androgen* adj (replac* or substitut* or supplement* or therap* or treatment* or cream$1 or gel or gels or implant* or inject* or patch*)).tw. (6312)
7 (androgen* adj3 (buccal* or oral* or transdermal*)).tw. (632)
8 TRT.tw. (2125)
9 (testosterone adj (beta cyclopentylpropionate or cyclopentylpropionate or cipionate or cypionate or enanthate or enanthane or ethanate or heptonate or heptylate or oenanthate or undecanoate or undecylate or "17 undecylate")).tw. (2636)
10 ("8-Isotestosterone" or andriol or "andro 100" or "androgyn LA" or androderm or androfort or androgel or androlin or andronaq or andropatch or androsorb or androstenolone or androtardyl or androtest or androtop or andrusol or axiron).tw. (1095)
11 ("Bio-T-Gel" or Ciclosterone or "Cristerona T" or "Cristerone T" or CompleoTRT or "CP 601B" or Delatestryl or Depandro or Deposteron or Depostomead or Depo-Testosterone or Depotest or Depovirin or Depoviron or Delatestryl or Duratest or Durathate or Everone or "first-testosterone" or Fortesta or Rortigel or Hexanecarboxylate or Histerone or Homosteron* or Intrinsa or Jenasteron or LibiGel or Livensa or Malerone or Malogen or Malogex or Mertestate).tw. (492)
12 (Nasobol or Nebido or "Neo-Hombreol F" or "Neo-testis" or Neotestis or "NSC 9700" or Opterone or Oreton or "Oreton-F" or Orquisteron).tw. (292)
13 (Pantestone or Perandren or Percutacrine androgenique or Percutacrine androgine or Pertestis or Primotest or Primoteston or Relibra or Restandol or Sterotate or Striant or Sustanon$1 or "Sustason 250" or Synandrol).tw. (674)
14 (Teslen or "Testa-C" or Testamone or Testandrone or Testaqua or Testerone or Testex or Testiculosterone or Testim or Testo Enant or Testobase or Testoderm or Testogel or Testoject-50 or Testolin or Testoluton or Testopel or Testopropon or Testosteroid).tw. (691)
15 (Testostosterone or Testoviron or Testrin or Testro or Testrone or Theramex or Tostrelle or Testryl or Tostrex or Trans-Testosterone).tw. (604)
16 (UNII-3XMK78S47O or Undestor or Virilon or Virormone or Virosterone or Vogelxo).tw. (61)
17 or/1-16 (39453)
18 exp Animals/ not (exp Animals/ and Humans/) (8702141)
19 17 not 18 (25517)
20 (controlled clinical trial or randomized controlled trial).pt. (457659)
21 clinical trials as topic.sh. (169995)
22 (randomi#ed or randomly or RCT$1 or placebo*).tw. (1423548)
23 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (296647)
24 trial.ti. (292735)
25 or/20-24 (1829141)
26 19 and 25 (3594)
27 (comment or editorial or interview or letter or news).pt. (2802584)
28 26 not 27 (3546)
29 (control* adj2 trial*).tw. (323672)
30 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (73609)
31 (nRCT or nRCTs or non-RCT$1).tw. (647)
32 (control* adj3 ("before and after" or "before after")).tw. (6046)
33 time series.tw. (33994)
34 (pre- adj3 post-).tw. (110642)
35 (pretest adj3 posttest).tw. (6260)

36 (control* adj2 stud$3).tw. (346641)
37 Control Groups/ (74764)
38 (control$ adj2 group$1).tw. (752277)
39 or/29-38 (1509227)
40 19 and 39 (2115)
41 40 not 27 (2097)
42 exp Cohort Studies/ (1517558)
43 cohort$1.tw. (675350)
44 Retrospective Studies/ (837256)
45 (longitudinal or prospective or retrospective).tw. (1721897)
46 ((followup or follow-up) adj (study or studies)).tw. (89267)
47 Observational study.pt. (2469)
48 (observation$2 adj (study or studies)).tw. (111012)
49 ((population or population-based) adj (study or studies or analys#s)).tw. (26131)
50 ((multidimensional or multi-dimensional) adj (study or studies)).tw. (187)
51 Comparative Study.pt. (1676994)
52 ((comparative or comparison) adj (study or studies)).tw. (185742)
53 or/42-52 (4729450)
54 19 and 53 (3389)
55 54 not 27 (3352)
56 28 or 41 or 55 (6587
57 56 use prmz (3219) [ALL MEDLINE RECORDS]
58 28 use prmz (1720) [MEDLINE RCTS]
59 41 use prmz (845) [MEDLINE NON-RCTS]
60 55 use prmz (1837) [MEDLINE OBSERV]
61 androgen therapy/ (3539)
62 androgen deficiency/dt (507)
63 testosterone undecanoate/ (1591)
64 testosterone cipionate/ (871)
65 testosterone enantate/ (2439)
66 (testosteron* adj3 (replac* or substitut* or supplement* or therap* or treatment* or buccal or cream$1 or gel or gels or implant* or inject* or oral* or patch* or transdermal*)).tw. (20369)
67 (androgen* adj (replac* or substitut* or supplement* or therap* or treatment* or cream$1 or gel or gels or implant* or inject* or patch*)).tw. (6312)
68 (androgen* adj3 (buccal* or oral* or transdermal*)).tw. (632)
69 TRT.tw. (2125)
70 (testosterone adj (beta cyclopentylpropionate or cyclopentylpropionate or cipionate or cypionate or enanthate or enanthane or ethanate or heptonate or heptylate or oenanthate or undecanoate or undecylate or "17 undecylate")).tw. (2636)
71 ("8-Isotestosterone" or andriol or "andro 100" or "androgyn LA" or androderm or androfort or androgel or androlin or andronaq or andropatch or androsorb or androstenolone or androtardyl or androtest or androtop or andrusol or axiron).tw. (1095)
72 ("Bio-T-Gel" or Ciclosterone or "Cristerona T" or "Cristerone T" or CompleoTRT or "CP 601B" or Delatestryl or Depandro or Deposteron or Depostomead or Depo-Testosterone or Depotest or Depovirin or Depoviron or Delatestryl or Duratest or Durathate or Everone or "first-testosterone" or Fortesta or Rortigel or Hexanecarboxylate or Histerone or Homosteron* or Intrinsa or Jenasteron or LibiGel or Livensa or Malerone or Malogen or Malogex or Mertestate).tw. (492)
73 (Nasobol or Nebido or "Neo-Hombreol F" or "Neo-testis" or Neotestis or "NSC 9700" or Opterone or Oreton or "Oreton-F" or Orquisteron).tw. (292)
74 (Pantestone or Perandren or Percutacrine androgenique or Percutacrine androgine or Pertestis or Primotest or Primoteston or Relibra or Restandol or Sterotate or Striant or Sustanon$1 or "Sustason 250" or Synandrol).tw. (674)
75 (Teslen or "Testa-C" or Testamone or Testandrone or Testaqua or Testerone or Testex or Testiculosterone or Testim or Testo Enant or Testobase or Testoderm or Testogel or Testoject-50 or Testolin or Testoluton or Testopel or Testopropon or Testosteroid).tw. (691)
76 (Testostosterone or Testoviron or Testrin or Testro or Testrone or Theramex or Tostrelle or Testryl or Tostrex or Trans-Testosterone).tw. (604)
77 (UNII-3XMK78S47O or Undestor or Virilon or Virormone or Virosterone or Vogelxo).tw. (61)
78 or/61-77 (33099)
79 randomized controlled trial/ or controlled clinical trial/ (936519)
80 exp "clinical trial (topic)"/ (104828)
81 (randomi#ed or randomly or RCT$1 or placebo*).tw. (1423548)
82 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (296647)
83 trial.ti. (292735)
84 or/79-83 (1962147)
85 78 and 84 (4042)
86 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (37422531)
87 exp humans/ or exp human experimentation/ or exp human experiment/ (28425359)
88 86 not 87 (8998814)
89 85 not 88 (3544)
90 (letter or editorial).pt. (2492646)
91 89 not 90 (3515)

Supplemental Online Content: Elliott et al. Testosterone therapy in hypogonadal men: a systematic review and network meta-analysis.

92 (control* adj2 trial*).tw. (323672)
93 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (73609)
94 (nRCT or nRCTs or non-RCT$1).tw. (647)
95 (control* adj3 ("before and after" or "before after")).tw. (6046)
96 time series analysis/ (13996)
97 time series.tw. (33994)
98 pretest posttest control group design/ (202)
99 (pre- adj3 post-).tw. (110642)
100 (pretest adj3 posttest).tw. (6260)
101 controlled study/ (4336835)
102 (control* adj2 stud$3).tw. (346641)
103 control group/ (74764)
104 (control* adj2 group$1).tw. (752277)
105 or/92-104 (5430128)
106 78 and 105 (7057)
107 106 not 88 (3849)
108 107 not 90 (3833)
109 cohort analysis/ (334727)
110 cohort$1.tw. (675350)
111 retrospective study/ (837256)
112 longitudinal study/ (153245)
113 prospective study/ (618128)
114 (longitudinal or prospective or retrospective).tw. (1721897)
115 follow up/ (824941)
116 ((followup or follow-up) adj (study or studies)).tw. (89267)
117 observational study/ (58475)
118 (observation$2 adj (study or studies)).tw. (111012)
119 population research/ (68859)
120 ((population or population-based) adj (study or studies or analys#s)).tw. (26131)
121 ((multidimensional or multi-dimensional) adj (study or studies)).tw. (187)
122 exp comparative study/ (2694962)
123 ((comparative or comparison) adj (study or studies)).tw. (185742)
124 or/109-123 (5973302)
125 78 and 124 (4650)
126 125 not 88 (3667)
127 126 not 90 (3625)
128 91 or 108 or 127 (7409)
129 128 use emczd (5052) [ALL EMBASE RECORDS]
130 91 use emczd (2221) [EMBASE RCTS]
131 108 use emczd (3091) [EMBASE NON-RCTS]
132 127 use emczd (2341) [EMBASE OBSERV]
133 58 or 130 (3941) [MEDLINE/EMBASE RCTS]
134 remove duplicates from 133 (2771) [UNIQUE RCTS]
135 134 use prmz (1666) [MEDLINE UNIQUE RCTS]
136 134 use emczd (1105) [EMBASE UNIQUE RCTS]
137 59 or 131 (3936) [MEDLINE/EMBASE NON-RCTS]
138 137 not 133 (1817) [OVERLAP REMOVED]
139 remove duplicates from 138 (1633) [UNIQUE NON-RCTS]
140 139 use prmz (264) [MEDLINE UNIQUE NON-RCTS]
141 139 use emczd (1369) [EMBASE UNIQUE NON-RCTS]
142 60 or 132 (4178) [MEDLINE/EMBASE OBSERV]
143 142 not (133 or 137) (2513) [OVERLAP REMOVED]
144 remove duplicates from 143 (2170) [UNIQUE OBSERV]
145 144 use prmz (1216) [MEDLINE UNIQUE OBSERV STUDIES]
146 144 use emczd (954) [EMBASE UNIQUE OBSERV STUDIES]
147 134 or 139 or 144 (6574) [UNIQUE RECORDS – ALL STUDY TYPES]

eAppendix 2: Scales represented in the analysis of data for each outcome

Qualtiy of life	Aging Males' Symptoms
	Minnesota Living with Heart Failure Questionnaire
	Quality of Life Specific to Male Erection Difficulties
	International Prostate Symptoms Score Quality of Life
	Quality of Life Enjoyment and Satisfaction Questionnaire
	Questions on Life Satisfaction, health subscale
	Health Related Quality of Life, sexual function domainSF-36 (total score)
Depression	Hospital Anxiety and Depression Scale
	Beck's Depression Inventory
	General Well-Being Index, depressed mood dimension
	Geriatric Depression Scale
	Hamilton Depression Scale
Libido	International Index of Erectile Function (sexual desire domain)
	Men's Sexual Health Questionnaire (sexual desire domain)
	Partial Androgen Deficiency in Aging Men (PADAM) Questionnaire
	Psychosexual Daily Questionnaire
Erectile function	International Index of Erectile Function (IIEF-5 or erectile function domain of IIEF-15)

eAppendix 3: Included studies*

*The list of excluded studies is available from the authors on request.

Note: studies were not evaluated for inclusion on the basis reported outcomes.

1. Agarwal PK, Oefelein MG. Testosterone replacement therapy after primary treatment for prostate cancer. *J Urol.* 2005; 173: 533–6.
2. Agledahl I, Brodin E, Svartberg J, et al. Impact of long-term testosterone treatment on plasma levels of free TFPI and TF-induced thrombin generation ex vivo in elderly men with low testosterone levels. *Thrombo Haemostasis*. 2009; 102: 945.
3. Agledahl I, Hansen JB, Svartberg J. Impact of testosterone treatment on postprandial triglyceride metabolism in elderly men with subnormal testosterone levels. *Scand J Clin Lab Invest* 2008; 68: 641.
4. Alamir MA, Ellenberg SS, Swerdloff RS, et al. The Cardiovascular Trial of the Testosterone Trials: Rationale, design, and baseline data of a clinical trial using computed tomographic imaging to assess the progression of coronary atherosclerosis. *Coronary Artery Disease.* 2016;27:95.
5. Amory JK, Watts NB, Easley KA, et al. Exogenous testosterone or testosterone with finasteride increases bone mineral density in older men with low serum testosterone. *J Clin Endocrinol Metab* 2004; 89: 503–10.
6. Andrade ES, Jr., Clapauch R, Buksman S. Short term testosterone replacement therapy improves libido and body composition. *Arq Bras Endocrinol Metabol* 2009;53:996–1004.
7. Arafa M, Zohdy W, Aboulsoud S, et al. Prevalence of late-onset hypogonadism in men with type 2 diabetes mellitus. *Andrologia* 2012; 44: 756.
8. Arver S, Sinha-Hikim I, Beall G, Guerrero M, Shen R, Bhasin S. Serum dihydrotestosterone and testosterone concentrations in human immunodeficiency virus-infected men with and without weight loss. *J Androl* 1999; 20: 611–8.
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eAppendix 4: Characteristics of the included RCTs and NRS

eTable 1: Characteristics of included RCTs that reported at least 1 outcome of interest

Author, year, page (companion publications)	Population*	Duration	Groups (no. randomized)	Age, yr, mean (SD);	Baseline Total T, mean (SD), nmol/L	Industry funding
Dias 2016, p. 1865 (Dias 2017 p.143; Dias 2016, p. 33; Dias 2017, p. 31)	Older men with low testosterone	12 mo	1% Gel, 50 mg/d (16) Placebo (13)	72 (SEM 1) 72 (SEM 1)	10.4 (1.9) 10.5 (2.1)	No
Chillaron 2016, p. 849	T1D	22 wk	IM TU 1000 mg/10 wk (6) Placebo (7)	47.9 (7.3) 45.2 (11.7)	12.4 (3.5) 9.9 (4.5)	Yes
Brock 2016, p. 699 (Maggi 2017, p. 1220)	≥ 1 symptom of testosterone deficiency	12 wk	2% Testosterone solution, 60 mg/d (358) Placebo (357)	54.7 (10.6) 55.9 (11.4)	7.0 (2.3) 7.0 (2.3)	Yes
Dhindsa 2016, p. 82	T2DM	24 wk	IM TC, 250 mg/2wk (22) Placebo (22)	54.6 (7.9) (NR by group)	8.7 (2.8) (NR by group)	No
Konaka 2016, p. 25 (Shigehara 2017, p. 1; Shigehara 2015, p. 169)	Late onset hypogonadism	52 wk	IM TE, 250 mg/4 wk (169) No treatment (165)	65.7 (9) 67.6 (9.4)	Free T 7.1 (3.2) 6.7 (3.5) pg/ml	No
Magnussen 2016, p. 980	T2DM	24 wk	1% gel, 50 mg/d (22) Placebo (21)	61 (6) 59 (6)	7.1 (95%CI 6.6-11.9) 9.4 (95%CI 8.1-12.5)	Yes
Ng Tang Fui 2016, p. 153 (Ng Tang Fui 2017, p. 420)	BMI ≥ 30	56 wk	IM TU, 1000 mg/10 wk (49) Placebo (51)	54.3 (IQR 47.3-59.8) 52.8 (IQR47.6-60.1)	8.2 (2.5) 8.4 (2.3)	Yes
Sinclair 2016, p. 906	Cirrhosis	54 wk	IM TU, 1000 mg/12 wk (50) Placebo (51)	55.5 (IQR 52-60) 54.0 (IQR 50-59)	9.3 (IQR 3.9-17) 9.1 (2.7-12.7)	Yes
Snyder 2016 p. 611† (Cunningham 2016, p. 3096; Snyder 2017, p. 471; Roy 2017, p. 480; Resnick 2017, p. 717; Cunningham 2015, p. 1146; Abd Alamir 2016, p. 95; Swerdloff 2015, p. 3280; Budoff 2017,	Older men with decreased libido or sexual function (Sexual function trial); limited mobility (Physical function trial); low vitality (Vitality trial)	12 mo	1% gel, 50 mg/d (395) Placebo (395)	72.1 (5.7) 72.3 (5.8)	232 (63) 236 (67)ng/dL	Mix

p. 708)						
Basaria 2015, p. 570 (Storer 2017, p. 583)	Older men	3 yr	1% gel, 75 mg/d (156) Placebo (152)	66.9 (5.0) 68.3 (5.3)	10.7 (2.2) 10.7 (2.3)	Yes
Basaria 2015, p. 280 (Huang 2016, p. 232)	Opioid-induced hypogonadism	12 wk	1% gel, 50 mg/d (43) Placebo (41)	48 (9) 50 (6)	8.2 (3.4) 7.7 (3.0)	Yes
Cherrier 2015, p. 421	Mild cognitive impairment	6 mo	Gel, 50-100 mg/d (10) Placebo (12)	70.5 (8.2)	10.7 (3.2) 9.8 (2.7)	Mix
Paduch 2015, p.2956	Ejaculatory dysfunction	16 wk	2% solution, 60 mg/d (36) Placebo (40)	48.4 (9.8) 52.7 (9.3)	7.4 (1.9) 7.7 (1.8)	Yes
Borst 2014, p. E433	Hypogonadal men	12 mo	Placebo (16) IM TE, 125 mg/wk (14)	70.8 (9.7) 69.2 (8.0)	8.5 (10.1) 9.2 (11.9)	Mix
Gianatti 2014, p. 2098 (Gianatti 2014, p. 3821; Gianatti 2016, p. 55)	Type 2 diabetes	40 wk	Placebo (43) IM TU, 1000 mg/12 wk (45)	62 (7.4) 62 (8.1)	8.5 (2.8) 8.7 (3.0)	Yes
Hackett 2013, p.1891 (Hackett 2013, p. 1612, Hackett 2014)	T2DM and symptoms of hypogonadism	30 wk	Placebo (102) IM TU, 1000 mg/12 wk (97)	62.0 (9.3) 61.2 (10.5)	8.9 (3.8) 9.2 (3.1)	Yes
Wang 2013, p. 1	Osteoporosis	24 mo	Placebo (62) Oral TU, 20 mg/d (62) Oral TU, 40 mg/d (62)	68.0 (4.8) 68.4 (5.5) 68.1 (5.4)	7.6 (0.7) 7.6 (0.9) 7.4 (0.8)	No
Behre 2012, p. 198	AMS score >36	6 mo	Placebo (179) 1% gel, 50 mg/d (183)	62.1 (6.3) 61.9 (6.6)	10.6 (2.6) 10.4 (2.6)	Yes
Spitzer 2012, p. 681 (Spitzer 2013)	Erectile dysfunction	14 wk	Placebo (70) 1% gel, 100 mg/d (70)	54.6 (8.5) 55.1 (8.3)	8.8 (2.4) 8.6 (2.2)	No
Stout 2012, p. 893	Chronic heart failure	12 wk	Placebo (20) Sustanon,‡ 100 mg/2 wk (20)	65.9 (8.8) 68.3 (5.3)	11.2 (2.6) 10.4 (2.7)	No
Zhang 2012, p. 3806	Positive score on ADAM questionnaire	6 mo	Vitamin E/C (80) Oral TU, 120 or 160 mg/d (based on T level at baseline)(80)	61.1 (7.1) 59.4 (6.3)	7.7 (0.8) 8.0 (0.7)	No
Ho 2011, p. 260 (Tan 2013, Tong 2012)	At least mild AMS symptoms	42 wk	Placebo (60) IM TU, 1000 mg/12 wk (60)	53.0 (8.2) 53.4 (7.4)	8.9 (2) 9.1 (1.8)	Yes
Jones 2011, p. 828	MetS or T2DM	12 mo	Placebo (112)	59.9 (9.4)	9.5 (3.3)	Yes

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(Stanworth 2014)	with at least 2 symptoms of hypogonadism		2% gel, 60 mg/d (108)	59.9 (9.1)	9.2 (2.6)	
Kaufman 2011, p. 2079	"otherwise healthy"	6 mo	Placebo (40) 1.62% gel, 40.5 mg/d (234)	55.5 (10.3) 53.6 (9.5)	10.2 (NR) 9.8 (NR)	Yes
Sheffield-Moore 2011, p. E1831 (Fitts 2015, p. E223)	Community-dwelling men	5 mo	Placebo (8) IM TE, 100 mg/wk (8)	65 (3) 73 (8)	11.8 (2.9) 11.9(2.9)	No
Shigehara 2011, p. 53	Benign prostate hypertrophy	12 mo	No treatment (26) IM TE, 250 mg/4 wk (26)	68.9 (9.1) 72 (6.5)	Free T, pg/ml 6.7 (1.9) 7.0 (1.7)	NR
Aversa 2010, p. 776	MetS or T2DM	6 mo	Placebo (10) Oral TU 160 mg/d (10) IM TU 1000 mg/12 wk (32)	55 (5) 57 (8) 58 (10)	11.1 (NR by group)	NR
Aversa 2010, p. 3495	MetS or T2DM	12 mo	Placebo (10) IM TU, 1000 mg/12wk (40)	57 (8) 58 (10)	9.0 (1.7) 8.33 (2.4)	NR
Basaria 2010, p. 109 (Bachman 2014, Huang 2013, Basaria 2013, Travison 2011; Storer 2016)	Limited mobility	6 mo	Placebo (103) 1% gel, 100 mg/d (106)	74 (5) 74 (6)	8.2 (2.3) 8.7 (2.0)	No
Kalinchenko 2010, p. 602 (Giltay 2010)	MetS	30 wk	Placebo (71) IM TU, 1000 mg/12wk (113)	52.8 (9.67) 51.6 (9.76)	7.5 (5.2) 6.7 (3.0)	Yes
Kenny 2010, p. 1134	Low bone mass and frailty	12–24 mo	Placebo (62) 1% gel, 5 mg/d (69)	76.3 (8.0) 77.9 (7.3)	14.5 (6.7) 13.2 (6.2)	Mix
Srinivas-Shankar 2010, p. 639 (O'Connell 2010, Atkinson 2010)	Intermediate-frail and frail	6 mo	Placebo (136) 1% gel, 50 mg/d (138)	73.9 (6.4) 73.7 (5.7)	10.9 (3.1) 11 (3.2)	Yes
Caminiti 2009, p. 919 (Schwartz 2011)	Chronic heart failure	12 wk	Placebo (35) IM TU, 1000 mg/6 wk (35)	69 (66–74) 71 (67–76)	7.3 (7.3) 8.0 (6.2)	No
Chiang 2009, p. 467	Hypogonadal men	3 mo	Placebo (20) 1% gel, 50 mg/d (20)	NR	NR	NR
Emmelot-Vonk, 2009, p. 129 (Emmelot-Vonk 2008, Nakhai-Pour 2007, Buisson 2010)	Moderately low T levels	26 wk	Placebo (117) Oral TU, 160 mg/d (120)	67.4 (4.9) 67.1 (5.0)	10.4 (1.9) 11.0 (1.9)	No

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Heufelder 2009, p. 726	MetS and T2DM	52 wk	Placebo (16) 1% gel, 50 mg/d (16)	55.9 (6) 57.3 (5.6)	10.4 (0.8) 10.5 (0.8)	Yes
Hohl 2009, p. 989	High AMS score	12 or 14 wk	IM TU, 1000 mg/6 wk (10) IM TC, 200 mg/4wk (11) Durateston, IM, 250 mg/4wk (11)	59.6 (8.9) 59.6 (7.1) 60.4 (8.8)	9.9 (1.1) 10.1 (1.1) 9.9 (1.5)	No
Mathur 2009, p. 443	Chronic angina pectoris	12 mo	Placebo (7) IM TU, 1000 mg/12 wk (8)	67.8 (7.9) 62.1 (5.2)	10.1 (2.8) 9.8 (1.9)	Yes
Morales 2009, p. 104	Sexual dysfunction	4 mo	Placebo (29) Oral TU, 160 mg/d (29)	60.2 (9.6) 59.0 (10.6)	10.0 (5.5) 10.2 (4.9)	Yes
Shores 2009, p. 1009	Dysthymia or minor depression	12 wk	Placebo (16) 1% gel, 75 mg/d (17)	61.7 (7.0) 57.1 (5.7)	9.3 (3.4) 10.1 (3.7)	Mix
Agledahl 2008, p. 641	Subnormal total T	52 wk	Placebo (13) IM TU, 1000 mg/12 wk (14)	69.3 (5.0) 68.9 (5.4)	8.2 (2.4) 8.5 (1.7)	Mix
Basurto 2008, p. 140	Low total T	12 mo	Placebo (23) IM TE, 250 mg/3wk (25)	63.1 (7.7) 63.2 (8.5)	10.8 (1.3) 10.4 (1.1)	No
Raynaud 2008, p. 168	Hypogonadal men	6 mo	Patch, 4.8 mg/d(188) IM TE, 250 mg/3 wk (36)	42.0 (12.7) 40.7 (10.5)	4.6 (3.2 5.1 (3.3)	Yes
Svartberg 2008, p. 378	NR	12 mo	Placebo (19) IM TU, 1000 mg/12 wk (19)	69 (5) 69 (5)	8.2 (2.1) 8.4 (1.7)	Mix
Chiang 2007, p. 411	Hypogonadal men	3 mo	Placebo (20) 1% gel, 50 mg/d (20)	56.1 (14.6) 47.9 (17.0)	9.1 (6.9) 7.4 (5.6)	Yes
Brockenbrough 2006, p. 251	Hemodialysis-dependent end-stage renal disease	6 mo	Placebo (21) 1% gel, 100 mg/d (19)	53.0 (17.2) 58.9 (14.9)	7.0 (3.0) 7.6 (2.2)	Yes
Marks 2006, p. 2351	Symptoms of late-onset hypogonadism	6 mo	Placebo (22) IM TE, 150 mg/2wk (22)	68 (NR) 70 (NR)	8.7 (1.6) 7.7 (1.4)	Mix
Merza 2006, p. 381	Sexual dysfunction	6 mo	Placebo (19) Patch, 5 mg/d (20)	59.7 (10.2) 63.0 (9.0)	7.5 (2.5) 8.4 (3.3)	Yes
Kuhnert 2005, p. 317	Primary, secondary, LOH and symptoms of T deficiency	24 wk	Patch, 5 mg/d (52) 2.5%, gel, 125 mg/d (56) 2.5%, scrotal gel, 25 mg/d (54)	53 (IQR 16) 52.2 (IQR 22.5) 50 (IQR 21)	NR	Yes

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Orengo 2005, p. 20	Treatment-resistant depression	12 wk	Placebo (5) 1% gel, 50 mg/d (7)	63 (8.5) (NR by group)	8.9 (1.7) 10.2 (2.3)	No
Amory 2004, p. 503 (Page 2005, Vaughan 2007)	T below the range of normal for young adult men	36 mo	Placebo (24) IM TE 200 mg/2wk (24)	71 (4) 71 (4)	10.1 (2.1) 9.9 (1.6)	No
Cavallini 2004, p. 641	Symptoms of androgen decline	6 mo	Placebo (45) Oral TU, 160 mg/d (40)	63 (NR) 64 (NR)	10.5 (2.1) 9.9 (1.8)	No
Schubert 2004, p. 5429 (Jockenhovel 2009, Jockenhovel 2009, Minnemann 2008)	Primary or secondary hypogonadism	30 wk	IM TU, 1000 mg/9 wk (20) IM TE, 250 mg/3 wk (20)	41.1 (13.4) 36.3 (12.3)	3.9 (4.4) 2.7 (2.3)	Mix
Shabsigh 2004, p. 658 (Burnett 2013, Wang 2001, Swerdloff 2000)	Erectile dysfunction not responsive to sildenafil	12 wk	Placebo (36) 1% gel, 50 mg/d (39)	59.1 (9.4) 56.8 (10.2)	65% had T < 10.4 (NR by group)	Yes
Boyanov 2003, p. 1	T2DM, obesity, and "symptoms of andropause or erectile dysfunction"	3 mo	No treatment (24) Oral TU, 120 mg/d (24)	All: 57.5 (4.8) (NR by group)	10.76 (11.20) 9.56 (2.33)	NR
McNicholas 2003, p. 69	≥ 1 symptoms of "low T"	90 d	Patch, 5 mg/d (68) 1% gel, 50 mg/d (68) 1% gel, 100 mg/d (72)	57.9 (10.2) 59.0 (9.5) 56.7 (10.3)	7.90 (2.2) 7.95 (2.2) 7.92 (2.4)	Yes
Steidle 2003, p. 2673 (Seftel 2004)	≥ 1 symptoms of "low T"	90 d	Placebo (99) Patch, 5 mg/d (102) 1% gel, 50 mg/d (99) 1% gel, 100 mg/d (106)	56.8 (10.8) 60.5 (9.7) 58.1 (9.7) 56.8 (10.6)	7.9 (2.8) 8.3 (2.4) 8.1 (2.0) 8.1 (2.1)	Yes
Tan 2003, p. 13	Alzheimer's disease	12 mo	Placebo (5) IM TE, 200mg/2wk (5)	68.9 (NR) 72.4 (NR)	NR 3.6 (NR)	No
Ferrando 2002, p. 358 (Ferrando 2003)	"Healthy older men"	6 mo	Placebo (5) IM TE 50–400 mg/wk (7)	67 (6.7) 68 (7.9)	9.8 (4.3) 12.4 (4.4)	No
Kang 2002, p. 862	Coronary artery disease	12 wk	Placebo 17) Oral TU, 160 mg/d (18)	58 (9) 57 (7)	Free T, pg/ml 13.8 (1.8) 9.9 (3.1)	NR
Simon 2001, p. 2149	Healthy adult	3 mo	Placebo (6)	55.4 (3.6)	9.4 (1.0)	NR

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	men		Gel, 125 mg/d (6)	52.8 (4.2)	8.3 (0.3)	
Bhasin 2000, p. 763	HIV-infected with weight loss	16 wk	Placebo (14) IM TE, 100 mg/wk (17)	41.8 (9.4) 40.8 (4.9)	6.1 (2.9) 7.1 (3.0)	No
Wang 2000, p. 2839	Primary, secondary or late-onset hypogonadism	90 d	Patch, 5 mg/d (76) 1% gel, 50 mg/d (76) 1% gel, 100 mg/d (78)	51.1 (NR) 51.3 (NR) 51.0 (NR)	8.2 (4.8) 8.2 (4.6) 8.6 (4.8)	Mix
Clague 1999, p. 261	Community-living	3 mo	Placebo (7) IM TE, 200 mg/2wk (7)	65.3 (1.8) 68.1 (6.6)	11.6 (0.9) 11.3 (1.7)	No
Dobs 1999, p. 3469	Receiving TRT for at least 3 mo	24 wk	Patch, 5 mg/d (33) IM TE, 200 mg/2wk (33)	44.3 (11.1) 44.9 (11.6)	5.8 (2.7) 6.3 (3.3)	Mix
Bhasin 1998, p. 3155 (Arver 1999)	HIV	12 wk	Placebo (21) Patch, 5 mg/d (20)	NR	7.3 (2.9) 9.0 (1.7)	Mix
Grinspoon 1998, p. 18 (Grinspoon 2000)	AIDS wasting syndrome	6 mo	Placebo (26) IM TE, 300 mg/3wk (26)	44 (9) 40 (7)	10.1 (6.4) 11.3 (5.4)	No
Jockenhovel 1997, p. 2510	Primary or secondary androgen deficiency	12 wk	IM TE, 250 mg/3 wk (10) Pellets, 1200 mg (12)	30.0 (7.3) 36.3 (11.1)	1.6 (1.3) 1.9 (1.1)	NR
Jockenhovel 1997, p. 293 (Jockenhovel 1999, Schubert 2001)	Primary or secondary androgen deficiency	210 d	Oral TU, 160 mg/d (13) IM TE, 250 mg/3wk (15) Pellets, 1200 mg (15)	34.5 (14.1) 31.8 (10.1) 35.8 (10.4)	2.9 (1.4) 2.3 (2.3) 2.7 (1.5)	NR
Sih 1997, p. 1661	Community-dwelling healthy men	12 mo	Placebo (15) IM TC, 200 mg/2wk (17)	68 (6) 65 (7)	8.1 (0.7) 10.2 (0.9)	NR

Note: ADAM = Androgen Deficiency of the Aging Male, AMS = Aging Males' Symptoms [scale], CI = confidence interval, IM = intramuscular, IQR = interquartile range, LOH = late onset hypogonadism, MetS = metabolic syndrome, NR = not reported, SD = standard deviation, T = testosterone, T1D, type 1 diabetes, T2DM = type 2 diabetes mellitus, TC = testosterone cypionate, TE = testosterone enanthate, TRT = testosterone replacement therapy, TU = testosterone undecanoate.
*All RCTs involved men that were either described as hypogonadal and met the cut-off for hypogonadism (total T < 12 nmol/L or free T < 225 pmol/L) or reported total or free T below these cut-off points.
†The Testosterone Trials were a coordinated set of seven trials. In order to enroll, participants had to qualify for at least one of the Sexual Function Trial, Physical Function Trial, or the Vitality Trial (NCT00799617).
‡Blend of testosterone propionate, testosterone phenylpropionate, testosterone isocaproate, and testosterone decanoate.

eTable 2: Characteristics of included non-randomized studies that reported at least one outcome of interest

Study	Population*	Duration	Group (no. in group)	Age, yr, mean (SD)	Baseline total T, mean (SD), nmol/L†	Industry funding
Retrospective cohort						
Cheetham 2017, p. 491	≥ 40 yrs with documented androgen deficiency	Mean follow-up: 4.4 years (mean)	TRT (injection, oral, topical), dose NR (8808) Never-TRT (35527)	58.4 (NR) 59.8 (NR)	TRT group: 7.4 (IQR 5.5-8.8)**	No
Layton 2015, p. 1187	New users of TRT‡		Gel (114,918) Injection (111,354) Patch (9,906)	Range: 52.4 (15.1) to 72.7 (6.7)§	NR††	No
Pastuszak 2015, p. 165	New TRT users or had been off TRT for ≥ 3 or mo	26.2 (10.6) 29.8 (8.8) 28.2 (8.6) mo	Gel (1% 50–100 mg/d and 1.62% 20.25–80.1 mg/d) (47) IM TE or TC, 100–200mg/wk (57) Pellets, 75 mg/3–6 mo (74)	54.1 (9.8) 42.5 (12.3) 53.8 (13.0)	10.4 (3.1) 10.6 (5.7) 9.3 (5.8)	No
Ramasamy 2016	≥ 65 yr and ≥3 hypogonadal symptoms	3.4-3.8 yr	TRT, dose NR (153) No treatment (64)	74 (6.3) 75(6)	NR	NR
Aydogdu 2013, p. 243	IHH	24 wk	Sustanon, ¶ IM 250 mg/3wk (28) 1% gel, 50 mg/d (24)	20.9 (1.4) 21.3 (1.6)	0.9 (0.6) 1.4 (1.3)	No
Vigen 2013, p. 1829	Men who underwent coronary angiography at a VA medical centre	Mean follow-up: 840 d	TRT, dose NR (1223) No treatment (7486)	60.6 (7.6) 63.8 (9.0 yr)	6.1 (2.2) 7.2 (2.6)	NR
Shores 2012, p. 2050	> 40 yr treated at a VA medical center	20.2 (16.7) mo	TRT, dose NR (398) No treatment (633)	62.1 (10.6)	5.6 (2.2) 6.7 (1.9)	No
Rhoden 2006, p. 201	Hypogonadal men with negative prostate biopsy prior to initiation of TRT	12 mo	IM TRT, dose NR (33) 1% ge, dose NR (25)	58.3	10.3 (5.4) 10.2 (3.1)	No
Guay 2000, p. 132	Men with ED and primary or secondary hypogonadism	2-3 mo	IM TE, 200–300 mg/2-3 wk (25) Patch, 5 mg/d (16)	40–80	Free T: 8.1–9.7 pg/ml	NR
Hajjar 1997, p. 3793	Elderly men	24 mo	IM TE or TC, IM 200 mg/2 wk (45) No treatment (27)	71.8 (SE 1.7) 69.9 (SE 1.9)	10.8 (4.7) 9.6 (3.8)	NR
Prospective cohort						
Debruyne	≥18 years with a	36 mo	TRT, dose NR (750)	58.9 (10.3)	8.3 (3.9)	Yes

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2017, p. 216	diagnosis of hypogonadism		No TRT (249)	59.7 (11.1)	9.4 (3.7)	
Traish 2016, p. 1	Symptoms of hypogonadism	Up to 8 yr	IM TU, 1000 mg/12wk (360) No TRT (296)	57.4 (7.3) 64.8 (4.3)	9.8 (1.3) 9.6 (1.2)	Yes
Yassin 2017, p. 1	Treated or untreated hypogonadal men	6 yr	TRT, dose NR (42) No treatment (162)	61.3 (4.7)	≤ 12.1 7.1 (2.3)	NR
Jung 2016, p. 194	Symptoms of hypogonadism	8 mo	TU, 1000 mg/3 mo + lifestyle modification (54) Lifestyle modification (52)	56.7 (12.6) 57.8 (11.4)	8.7 (2.1) 9 (2.4)	No
Francomano 2014, p. 401	Severely obese men (mean BMI 42) with ≥ symptoms of hypogonadism	54 wk	DPE (12) DPE + IM TU, 1000 mg/12 wk (12)	53 (8) 56 (9)	8.2 (1.8) 8.5 (1.8)	NR
Blick 2013, p. 30	HIV/AIDS	12 mo	1% gel (Androgel), 50 mg/d (92) 1% gel (Testim), 50 mg/d (75)	49.5 (8.1)	13.9 (5.5) 13.7 (7.2)	Yes
Aversa 2012, p. 96	Middle-aged men with LOH and MetS	36 mo	IM TU, 1000 mg/12 wk (40) No treatment (20)	58 (10) 57 (8)	8.3 (2.4)	NR
Dean 2005, p. 87	21–81 yr	Up to 12 mo	1% gel, 50 mg/d (NR) 1% gel, 100 mg/d (NR)	58.5 (10.0)	8.1 (2.1)	NR
Wang 2004, p. 2085 (Swerdloff 2003 p.207)	19–68 yr	36 mo	1% gel, 50 mg/d (NR) 1% gel, 75 mg/d (NR) 1% gel, 100 mg/d (NR)	51.5 (0.9)	14.1 (1.3) 22.4 (2.7) 25.6 (2.4)	No

Note: DPE = diet plus exercise, ED = erectile dysfunction, IHH = Idiopathic hypogonadotropic hypogonadism, IM = intramuscular, IQR = interquarile range, LOH = late-onset hypogonadism, MetS = metabolic syndrome, NR = not reported, SE = standard error, SD = standard deviation, T = testosterone, TC = testosterone cypionate, TE = testosterone enanthate, TRT = testosterone replacement therapy, VA = Veterans Affairs.

*All studies involved men that were either described as hypogonadal and met the cut-off for hypogonadism (total T < 12 nmol/L or free T < 225 pmol/L) or reported total or free T below these cut-off points.

†Unless otherwise stated.

‡Full cohort includes patients with testosterone levels in the normal range; data extracted only for patients with total testosterone < 300 ng/dl (10.4 nmol/L).

¶Blend of estosterone propionate, testosterone phenylpropionate, testosterone isocaproate, and testosterone decanoate.

§Data provided separately for 3 databases. Range represents the high and low ages (SD) across the three databases.

**Baseline testosterone level not reported for the never-TRT group. In both the TRT group and the no TRT group, 98%–99% of patients had a total T level < 10.4 nmol/L at baseline.

††Mean total testosterone level not provide among patients with a "low" testosterone level (< 10.4 nmol/L).

eTable 3: Risk of bias of included randomized controlled trials that reported at least one outcome of interest

Author, year	Adequate sequence generation	Allocation concealment	Blinding of outcome assessment (objective outcomes)	Blinding of outcome assessment (subjective outcomes)	Incomplete outcome data addressed (efficacy outcomes)	Incomplete outcome data addressed (harm outcomes)
Dias 2016	Low	Unclear	Low	Low	High	Unclear
Chillarón 2016	Unclear	Low	Low	Unclear	Low	Low
Brock 2016	Low	Low	Low	Low	Low	Low
Dhindsa 2016	Unclear	Unclear	Low	Unclear	High	Unclear
Konaka 2016	Low	Unclear	Low	High	High	Unclear
Magnussen 2016	Low	Low	Low	Low	Low	Low
Ng Tang Fui 2016	Low	Low	Low	Low	High	Unclear
Sinclair 2016	Unclear	Low	Low	Low	High	High
Snyder 2016	Low	Low	Low	Low	Low	Low
Basaria 2015, p. 570	Unclear	Unclear	Low	Low	High	Unclear
Basaria 2015, p. 280	Low	Unclear	Low	Low	High	Unclear
Cherrier 2015	Unclear	Unclear	Low	Unclear	Low	Low
Paduch 2015	Low	Low	Low	Unclear	Low	Low
Gianatti 2014	Unclear	Low	Low	Low	Low	Low
Borst 2014	Low	Unclear	Low	High	High	High
Hackett 2013	Unclear	Low	Low	Low	Low	Low
Wang 2013	Unclear	Unclear	Low	NA	Low	High
Behre 2012	Low	Low	Low	Low	Low	High
Spitzer 2012	Unclear	Low	Low	Low	Low	Low
Stout 2012	Unclear	Unclear	NA	Low	High	High
Zhang 2012	Unclear	Low	Low	High	Low	Low
Ho 2011	Unclear	Low	Low	Low	Low	Low
Jones 2011	Unclear	Unclear	Low	Low	High	High
Kaufman 2011	Unclear	Low	Low	Low	High	Low
Sheffield-Moore 2011	Unclear	Low	Low	NA	Low	High
Shigehara 2011	Unclear	Unclear	Low	High	Low	Low

Aversa 2010, p. 776	Unclear	Unclear	Low	Low	Unclear	Unclear
Aversa 2010, p. 3495	Unclear	Unclear	Low	Low	Low	Low
Basaria 2010	Low	Low	Low	Low	Low	Unclear
Kalinchenko 2010	Unclear	Low	Low	Low	Low	Low
Kenny 2010	Unclear	Low	Low	Low	High	Unclear
Srinivas-Shankar 2010	Low	Low	Low	Low	Low	Unclear
Caminiti 2009	Unclear	Low	Low	Low	Low	Low
Chiang 2009	Unclear	Unclear	Low	Low	High	High
Emmelot-Vonk 2009	Low	Low	Low	Low	Low	Low
Heufelder 2009	Low	Unclear	Low	High	Low	Low
Hohl 2009	High	High	Low	High	Low	Low
Mathur 2009	Low	Unclear	Low	Low	Low	High
Morales 2009	Low	Low	Low	Low	Low	Low
Shores 2009	Low	Low	Low	Low	High	Unclear
Agledahl 2008	Unclear	Unclear	Low	NA	Low	Low
Basurto 2008	Low	Low	Low	Low	Low	Unclear
Raynaud 2008	Unclear	Unclear	Low	High	High	High
Svartberg 2008	Unclear	Unclear	Low	Low	Low	Unclear
Chiang 2007	Unclear	Unclear	Low	Unclear	High	Low
Brockenbrough 2006	Unclear	Low	Low	Unclear	High	Low
Marks 2006	Unclear	Unclear	Low	Low	Low	Low
Merza 2005	Unclear	Unclear	Low	Unclear	Low	Low
Kuhnert 2005	Unclear	Low	Low	High	High	High
Orengo 2005	Low	Unclear	Low	Unclear	High	High
Amory 2004	Low	Low	Low	Low	Unclear	Unclear
Cavallini 2004	Unclear	Unclear	Low	Unclear	Unclear	High
Schubert 2004	Low	Unclear	Low	High	Unclear	Low
Shabsigh 2004	Low	Unclear	Low	Low	Low	Unclear
Boyanov 2003	Unclear	Unclear	Low	High	Low	Low
McNicholas 2003	Unclear	Unclear	Low	High	High	High
Steidle 2003	Unclear	Unclear	Low	High	High	High
Tan 2003	Unclear	Unclear	Unclear	High	Low	Low
Ferrando 2002	Unclear	Unclear	Low	NA	Low	Low
Kang 2002	Unclear	Unclear	Low	NA	Low	Low
Simon 2001	Unclear	Unclear	Low	Low	NA	Low
Bhasin 2000	Low	Unclear	Low	Unclear	Low	Unclear
Wang 2000	Unclear	Unclear	Low	High	High	High

Clague 1999	Unclear	Unclear	Low	NA	Low	Low
Dobs 1999	Unclear	Low	Low	High	High	Unclear
Bhasin 1998	Unclear	Unclear	Low	Unclear	High	Unclear
Grinspoon 1998	Low	Low	Low	Low	High	Unclear
Jockenhovel 1997, p. 2510	Unclear	Unclear	Low	NA	Unclear	Unclear
Jockenhovel 1997, p. 293	Unclear	Unclear	Low	NA	Low	Unclear
Sih 1997	Low	Unclear	Low	Unclear	High	Unclear

Note: Risk of bias was not assessed for the studies that reported no outcomes of interest or that did not provide usable data (e.g., cross-over studies without first period data reported separately).

eTable 4: SIGN50 assessment of included non-randomized studies that reported at least one outcome of interest. Overall assessment was based on consideration of all domains of the SIGN50 Methodology checklist for cohort studies.

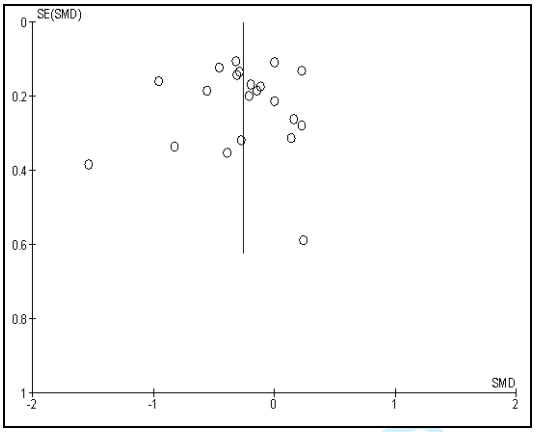
Study*	Overall assessment†	Comments
Traish 2017	Unacceptable (–)	Prospective cohort. Study "not designed or powered to address the effects of [TRT] on mortality in men with hypogonadism." Control group comprised men who opted against TRT. Did not adjust adjust for previous CV events, and groups were not balanced at baseline for some factors. Unclear from where participants were recruited and whether outcome assessment was blinded to exposure status. Outcomes assessed for up to 8 years.
Jung 2016	Unacceptable (–)	Prospective cohort. Did not report how study participants were assigned to treatment groups. No adverse events of interest reported (stroke, MI, prostate cancer). Unblinded, with 8 month treatment and follow-up
Debruyne 2017	Acceptable (+)	Prospective cohort (RHYME registry). Multinational registry of treated or untreated newly diagnosed hypogonadal men.Follow-up on 93% of cohort over 3-yr period. Included a wide age range and multiple comorbiditie but goups not well balanced across all baseline characteristics. Men with a history of prostate cancer were excluded. Outcome assessment blinded to exposure status.
Layton 2015	Acceptable (+)	Retrospective cohort. Comparative safety of TRT products grouped by route of administration (no comparison to non-users). Data unavailable for some patient characteristics. Study included a "large diverse patient sample representing men across age groups, populations, treatment and practice patterns, and health care systems." Unclear whether outcome assessment was blinded to exposure status. Mean treatment duration between 96 and 122 days.
Cheetham 2017	Acceptable (+)	Retrospective cohort. Cohort entry determind by dispensation of a TRT product. Over 50% of cohort prescribed an intramuscular TRT. Possible confounding by indication, analysis could not adust for all CV risk factors, and dose and duration of TRT were not considered. Unclear whether outcome assessment was blinded to exposure status. Length of follow up about 1 year longer for no TRT group.
Yassin 2017	Unacceptable (–)	Prospective registry. Investigation and biopsy frequency equal in both groups. Outcome assessment not blinded to exposure status. Percentage of cohort for whom data were available not reported. Confounding not considered.
Pastuszak 2015	Unacceptable (–)	Retrospective cohort. Considerable variation in baseline characteristics between groups, and confounding not considered. Outcome assessment not blinded to exposure status. 36 month follow-up.
Ramasay 2015	Unacceptable (–)	Retrospective cohort. "All major adverse cardiovascular events were verified by telephone with the patient (or family members if patient died)." Authors did not provide clear description and measurement about the outcomes. Median follow-up 3.8 (TRT) or 3.4 (no TRT) yr Confounding not considered, and outcome assessment not blinded to exposure status.
Francomano 2014	Unacceptable (–)	Prospective cohort. Obese men with low testosterone. Baseline characteristics were well matched on reported characteristics, but control group had contraindications to TRT. 33% dropout in treatment group, zero in control group;

		no comparison between those who dropped out or remained in study.
Aydogdu 2013	Acceptable (+)	Retrospective cohort. Men with IHH. SAE not defined as an outcome but reported that no SAEs were detected for any treatment group.
Blick 2013	Acceptable (+)	Prospective cohort. Groups were generally well matched on baseline characteristics with no statistically significant differences (except for study site). Patients in the 2 treatment groups were not followed for an equal length of time (Androgel: mean 6.1 yr; Testim: mean 1.9 yr). Skin reactions assessed but not reported. Outcome assessment was not blinded to exposure status.
Vigen 2013	Acceptable (+)	Retrospective cohort. All-cause mortality assessed via the Veterans Affairs vital status file. Myocardial infarction and ischemic stroke assessed via ICD-9 codes from Veterans Affairs inpatient treatment files. Conclusions based on a composite outcome. Sufficient data not reported to allow analysis of stroke or MI separately at each time point. Outcome assessment not blinded to exposure status.
Aversa 2012	Unacceptable (–)	Prospective cohort. Men with multiple sclerosis and late onset hypogonadism. Baseline characteristics were well matched but the control group comprised of men who had refused or had contraindications to testosterone. Adherence to treatment over 3 years was 50% in TU group. Those discontinuing TU but remaining in study for follow up were not included in efficacy analysis.
Shores 2012	Acceptable (+)	Retrospective cohort. Hazard ratio for mortality takes person-years of observation into account. Adjusted HR and CIs provided (adjusted for age, site, hospitalization in the past year, diabetes, coronary artery disease). Outcome assessment not blinded to exposure status. Exposure determined via Veterans Affairs pharmacy records and outcomes ascertained from 2 mortality databases.
Rhoden 2006	Acceptable (+)	Retrospective cohort. Patients had to have negative prostate biopsy before initiation of TRT, thus excluding any men with pre-existing large volume disease. Type and dose of IM testosterone not reported. Dose of gel not reported (data NR by type). Outcome assessment not blinded to exposure status.
Dean 2005	Unacceptable (–)	Prospective cohort. Poor reporting of the number of patients in each group and which group the safety events occurred in. Number of and reasons for withdrawals not reported. Safety data reported overall but not by treatment group. Outcome assessment not blinded to exposure status.
Wang 2004	Unacceptable (–)	Prospective cohort (open-label extension of an RCT). The number of men assigned to each group NR. Safety data poorly reported: 3 cases of prostate cancer reported but number of people in each group not reported. Outcome assessment not blinded to exposure status.
Guay 2000	Unacceptable (–)	Retrospective cohort. Safety data not reported by treatment group. Outcome assessment not blinded to exposure status.
Hajjar 1997	Unacceptable (–)	Retrospective cohort. Data not clearly provided. Safety outcomes were reported based on a subset of people assigned to each group, and it is not clear why the other patients were omitted. Outcome assessment not blinded to exposure status.

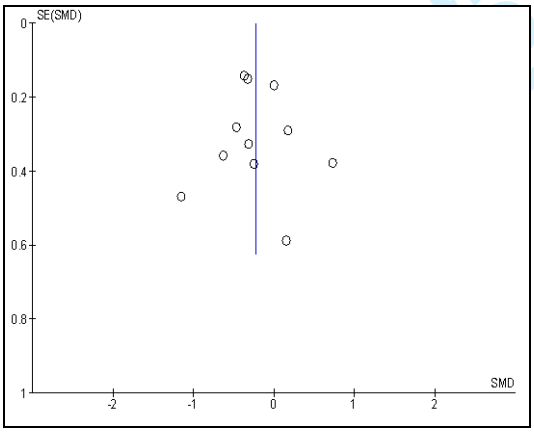
Note: CI = confidence interval, ICD = International Classification of Diseases, Ninth Revision, IHH = idiopathic hypogonadotropic hypogonadism, HR = hazard ratio, MI = myocardial infarction, NR = not reported, RCT = randomized controlled trial, SAE = serious adverse events, TRT = testosterone replacement therapy, TU = testosterone undecanoate.
*Non-randomized studies that reported at least 1 outcome of interest.
†Assessed by use of SIGN50 for cohort studies (www.sign.ac.uk/checklists-and-notes.html).

eAppendix 5: Funnel plots for assessment of publication bias

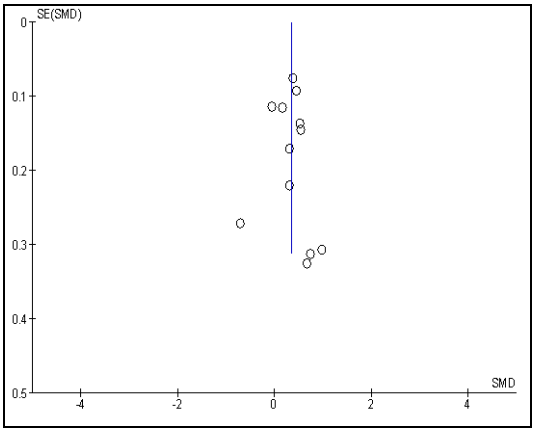
A) Quality of life



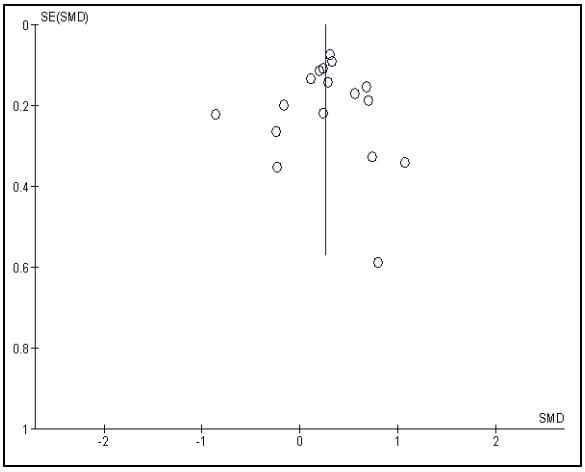
B) Depression



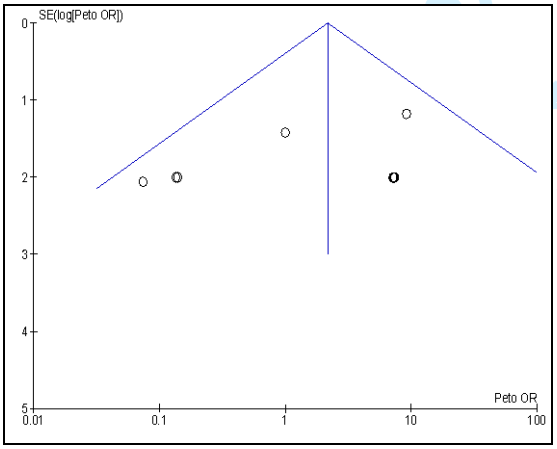
C) Libido



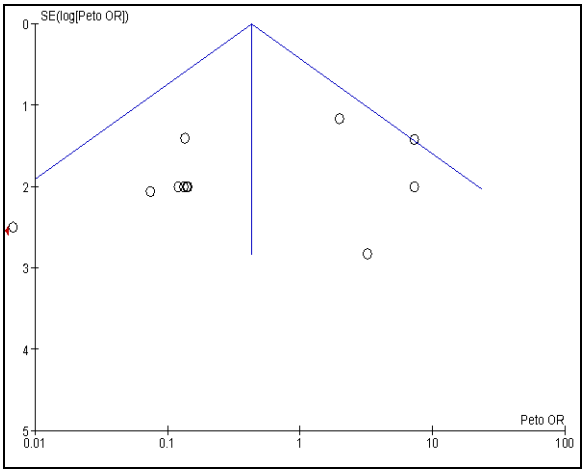
D) Erectile function



E) Cardiovascular death



F) Myocardial infarction



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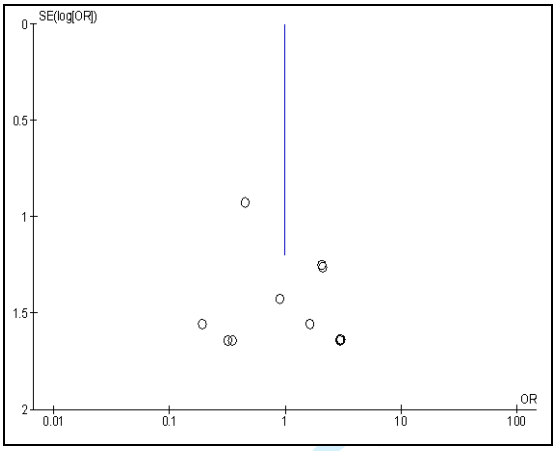
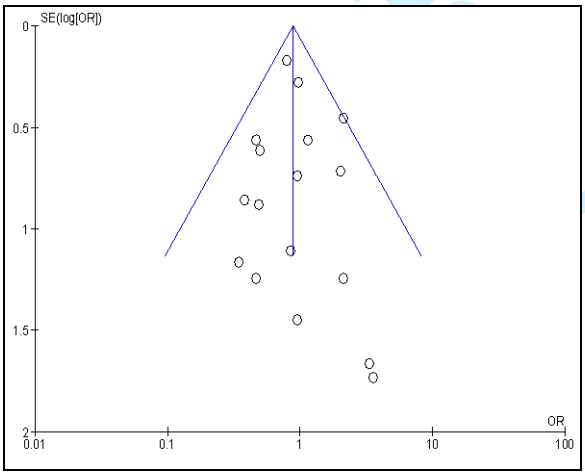
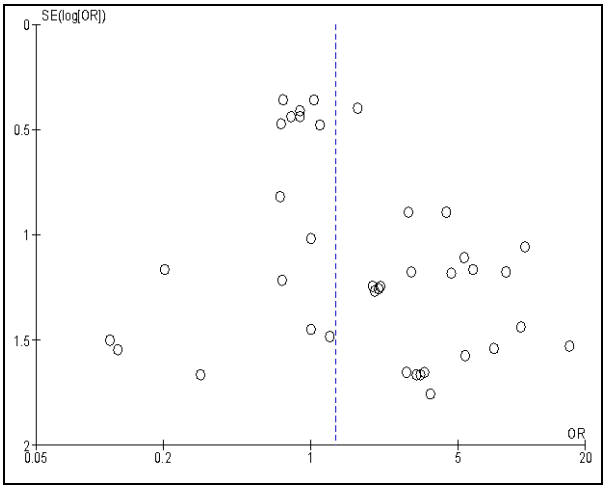
G) Prostate cancer



H) Serious adverse events



I) Withdrawals due to adverse events



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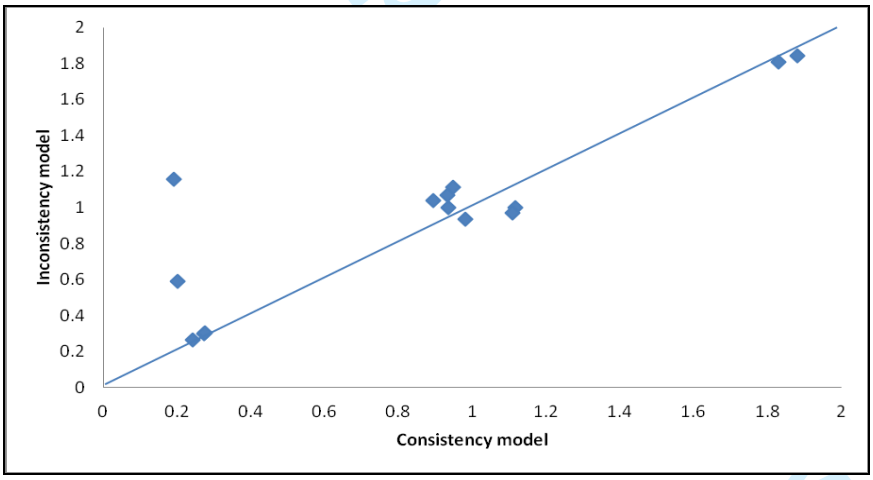
eAppendix 6: Evaluation of network consistency

We evaluated the consistency of networks with closed loops. To be classified as a "closed loop," at least 2 nodes had to be connected by more than one trial (e.g., not connected solely by a multi-arm trial).

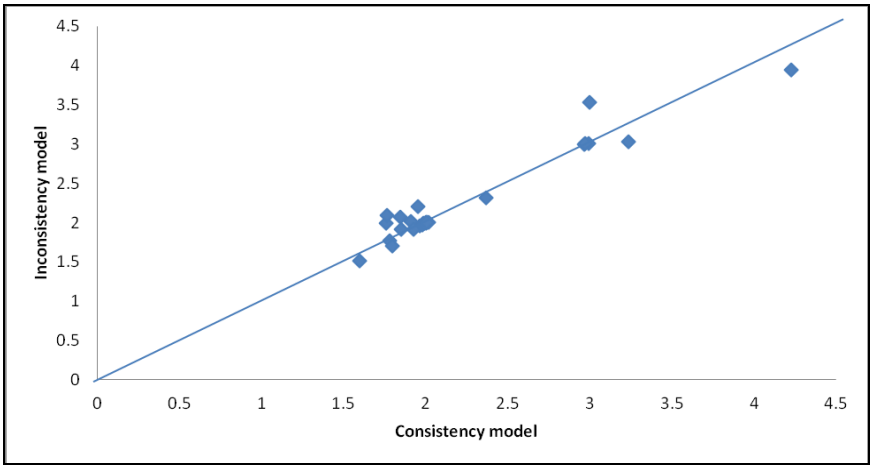
To evaluate the consistency of networks with closed loops, two analyses were performed. One was conducted using the standard consistency model, which assumes that the data in the network are consistent. A second analysis was performed using an inconsistency model, which assumes that the data in the network are not consistent. The posterior mean deviance of the individual data points derived from the inconsistency model was plotted against the posterior mean deviance derived from the consistency model. If inconsistency is present, data points will lie under the diagonal line, indicating deviation from the consistency model. Data points above the diagonal line indicate deviation from the inconsistency model and are not indicative of inconsistency.

Model fit was also evaluated by considering the residual deviance and deviance information criterion (DIC) of the inconsistency and consistency models, with the model that has the lower residual deviance and DIC representing the better fit for the data. For each network, the consistency model had a lower residual deviance and DIC for each outcome, representing better model fit.

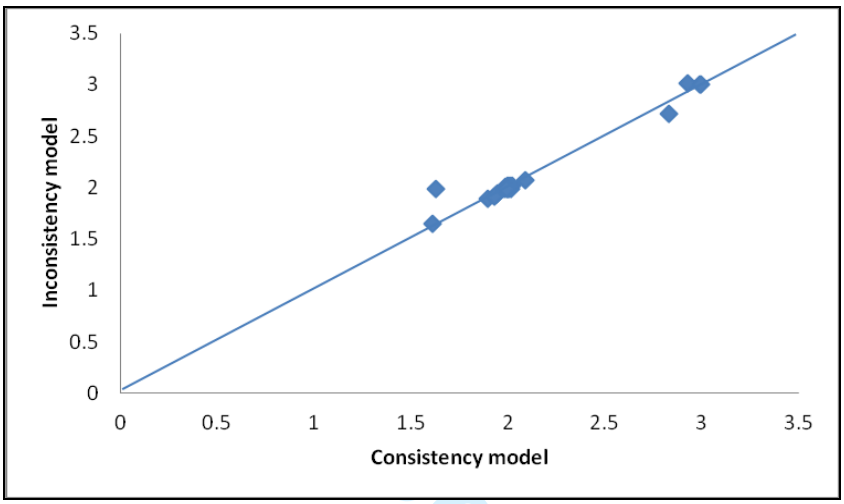
LIBIDO: BASE CASE (ALL STUDIES)



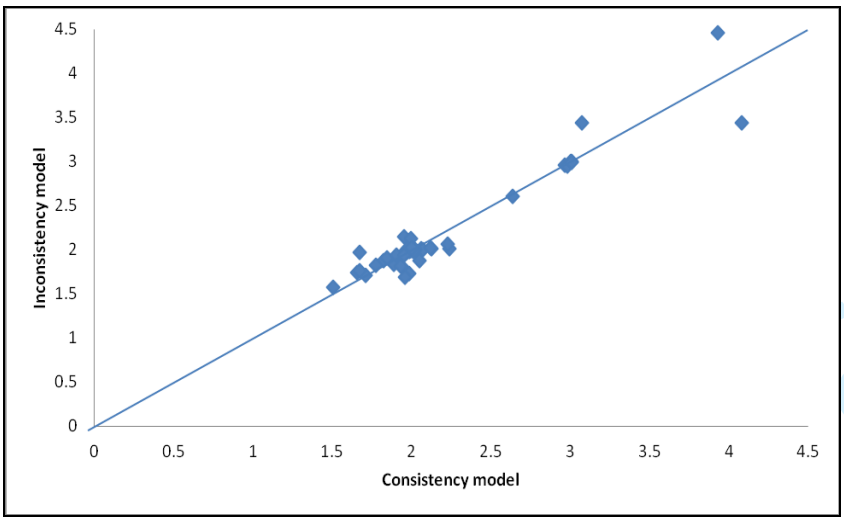
TOTAL TESTOSTERONE LEVEL, 3 MO



TOTAL TESTOSTERONE LEVEL, 6 MO



TOTAL TESTOSTERONE LEVEL, END OF STUDY



Supplemental Online Content: Elliott et al. Testosterone therapy in hypogonadal men: a systematic review and network meta-analysis.

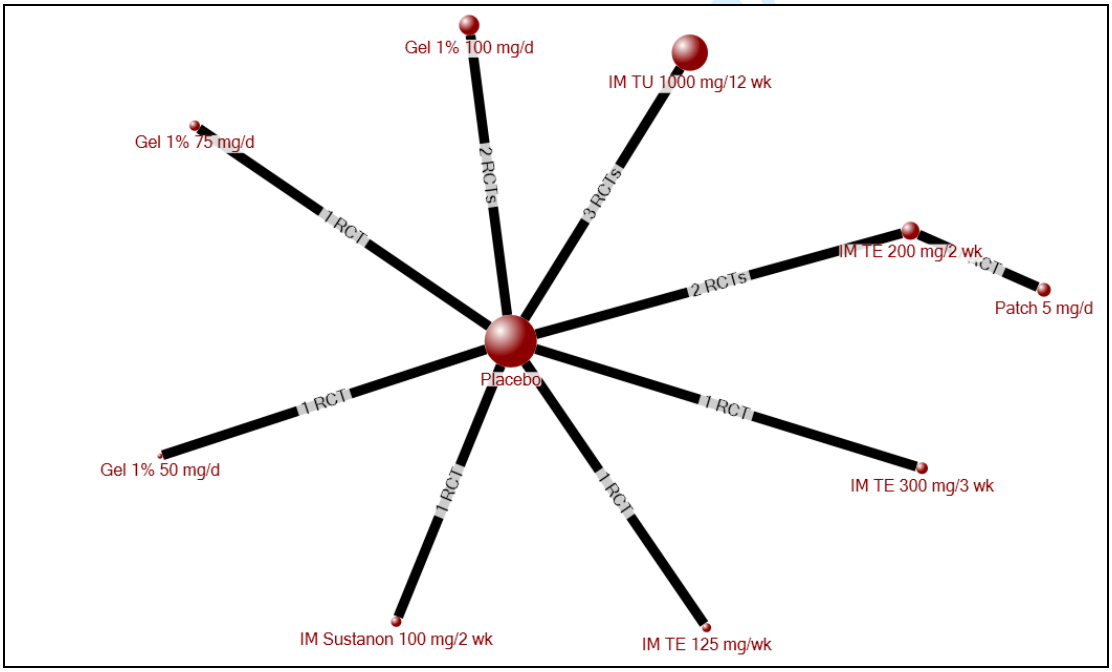
eAppendix 7: Evidence networks

Summary of network characteristics

Outcome	No. of trials	No. of treatments*	No. of comparisons†	No. of participants	Treatment duration
Quality of life	23	14	27	3090	12 wk to 3 yr
Depression	12	9	12	852	12 wk to 3 yr
Libido	14	10	23	3167	12 wk to 3 yr
Erectile function	17	9	19	3165	12 wk to 3 yr
Total testosterone, 3 mo	26	15	39	2739	NA
Total testosterone, 6 mo	23	18	29	2908	NA
Total testosterone, end of study	57	28	74	5538	12 wk to 3 yr
Serious AEs	15	7	15	1860	12 to 3 yr
Withdrawals due to AEs	27	16	29	4165	12 wk to 3 yr

Note: AE = adverse event.
*In addition to placebo
†Direct comparisons based on the number of 2-, 3-, and 4-arm trials.

eFigure 1A) Depression



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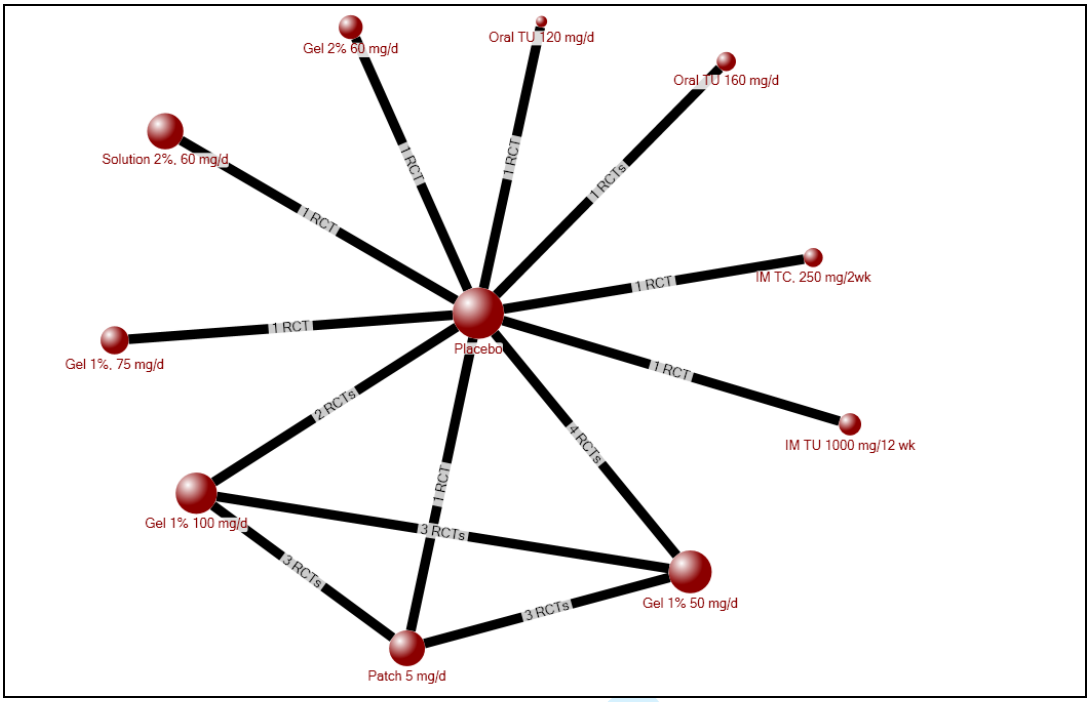
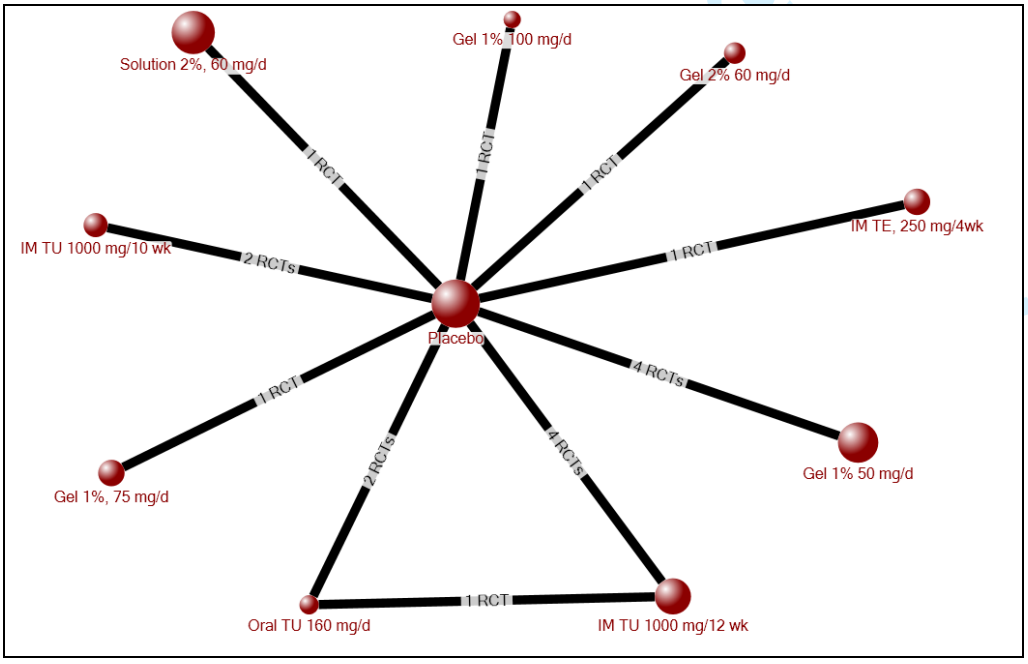
B) Libido



C) Erectile function



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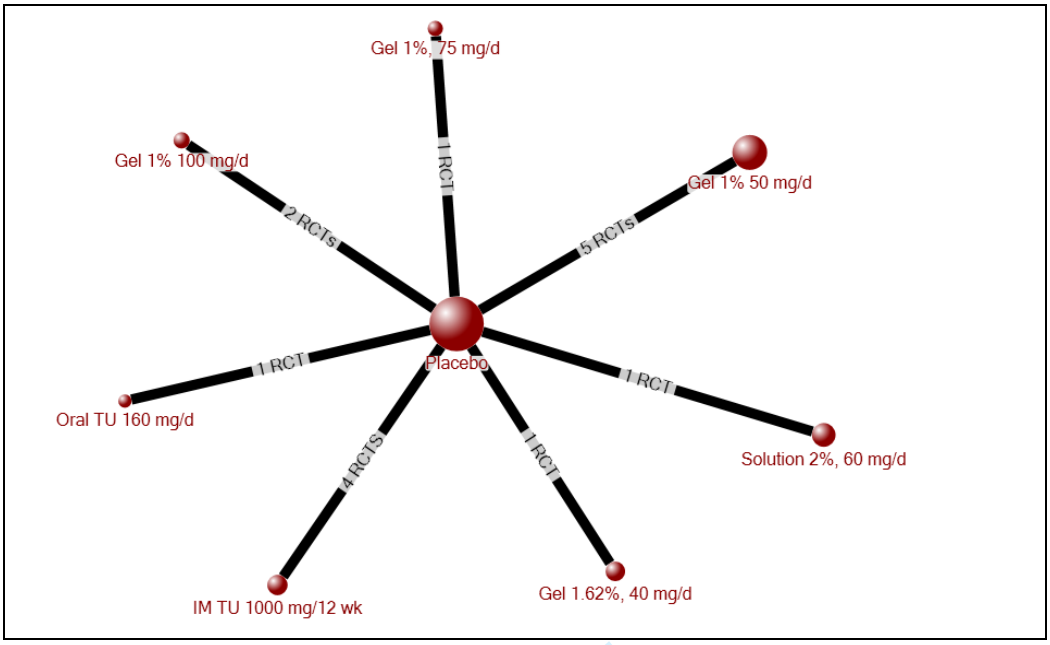
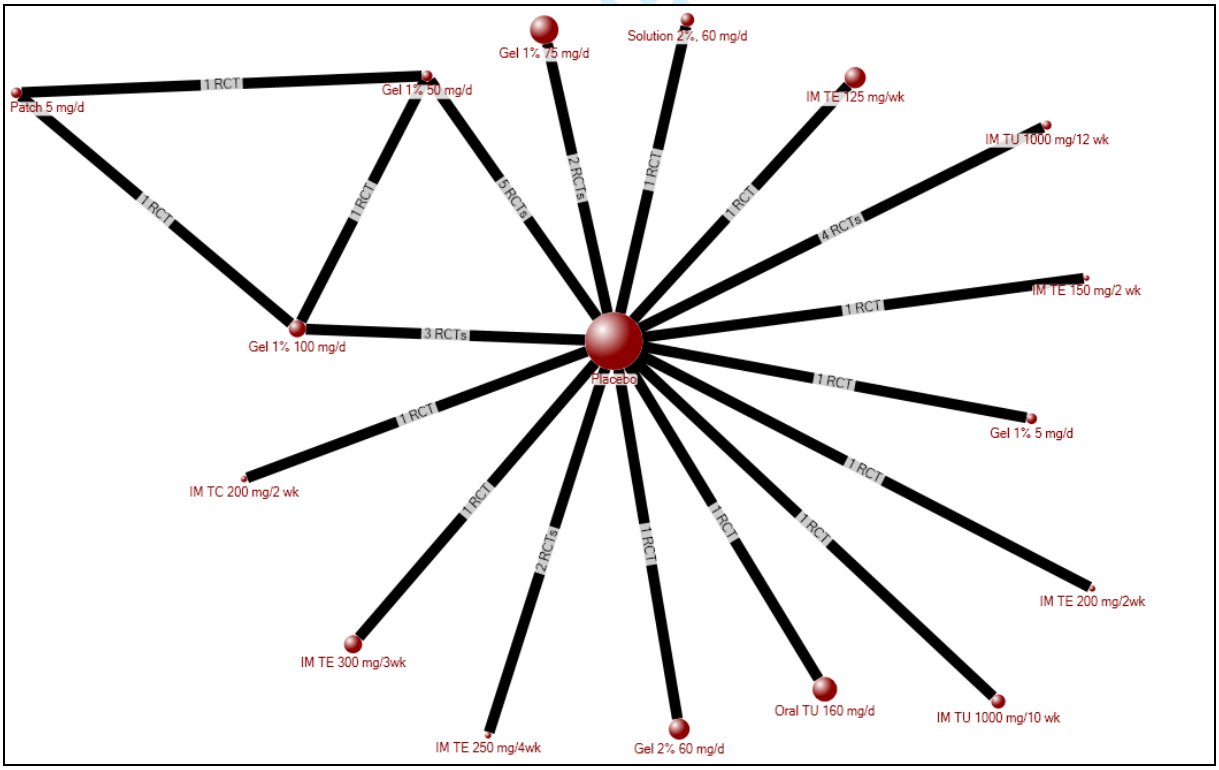
D) Serious adverse events



E) Withdrawals due to adverse events



Supplemental Online Content: Elliott et al. Testosterone therapy in hypogonadal men: a systematic review and network meta-analysis.

eAppendix 8: Pair-wise meta-analyses and network meta-analyses

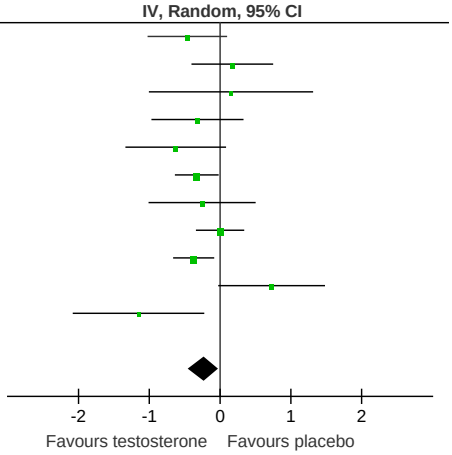
eFigure2: Individual trial results, depression

A) All trials

Study or Subgroup	Testosterone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Grinspoon 1998	-5.8	6.6	26	-2.7	6.6	26	9.2%	-0.46 [-1.01, 0.09]	1998
Amory 2004	-0.2	0.4	24	-0.3	0.7	24	8.9%	0.17 [-0.39, 0.74]	2004
Orengo 2005	-6	2.6	7	-6.8	6.9	5	3.0%	0.15 [-1.00, 1.30]	2005
Svartberg 2008	-1.3	2.9	19	-0.5	1.9	19	7.6%	-0.32 [-0.96, 0.32]	2008
Shores 2009	-4.3	3.1	17	-2.4	2.8	16	6.6%	-0.63 [-1.33, 0.07]	2009
Kalinchenko 2010	-3.6	5.3	113	-1.9	4.9	71	16.2%	-0.33 [-0.63, -0.03]	2010
Stout 2012	-3.8	6.1	15	-2.5	3.2	13	6.1%	-0.25 [-1.00, 0.49]	2012
Spitzer 2012	2	11.5	70	2	11.5	70	15.1%	0.00 [-0.33, 0.33]	2012
Hackett 2013	-1.1	3.9	97	0.4	4.1	102	16.9%	-0.37 [-0.65, -0.09]	2013
Borst 2014	1	2.2	14	-0.3	1.2	16	6.1%	0.73 [-0.02, 1.47]	2014
Cherrier 2015	-2.8	4.7	10	2.7	4.5	12	4.4%	-1.15 [-2.07, -0.23]	2015
Total (95% CI)			**412**			**374**	**100.0%**	**-0.23 [-0.44, -0.01]**	

Heterogeneity: Tau² = 0.05; Chi² = 17.84, df = 10 (P = 0.06); I² = 44%

Test for overall effect: Z = 2.08 (P = 0.04)

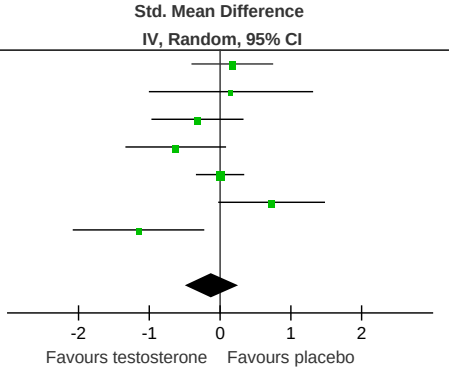


B) Trials involving men without major comorbidities

Study or Subgroup	Testosterone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Amory 2004	-0.2	0.4	24	-0.3	0.7	24	16.9%	0.17 [-0.39, 0.74]	2004
Orengo 2005	-6	2.6	7	-6.8	6.9	5	7.7%	0.15 [-1.00, 1.30]	2005
Svartberg 2008	-1.3	2.9	19	-0.5	1.9	19	15.3%	-0.32 [-0.96, 0.32]	2008
Shores 2009	-4.3	3.1	17	-2.4	2.8	16	14.0%	-0.63 [-1.33, 0.07]	2009
Spitzer 2012	2	11.5	70	2	11.5	70	22.6%	0.00 [-0.33, 0.33]	2012
Borst 2014	1	2.2	14	-0.3	1.2	16	13.2%	0.73 [-0.02, 1.47]	2014
Cherrier 2015	-2.8	4.7	10	2.7	4.5	12	10.4%	-1.15 [-2.07, -0.23]	2015
Total (95% CI)			**161**			**162**	**100.0%**	**-0.12 [-0.49, 0.26]**	

Heterogeneity: Tau² = 0.13; Chi² = 13.76, df = 6 (P = 0.03); I² = 56%

Test for overall effect: Z = 0.62 (P = 0.53)



eTable 5: Depression – Bayesian network meta-analysis*

Treatment	Standardized mean difference (95% confidence interval)									
	Placebo	Patch, 5 mg/d	Gel 1%, 50 mg/d	Gel 1%, 75 mg/d	Gel 1%, 100 mg/d	IM TU, 1000 mg/12 wk	IM TE, 125 mg/ wk	IM TE, 200 mg/ 3 wk	IM TE, 300 mg/ 3 wk	IM Sustanon, 100 mg/ 2 wk
Patch, 5 mg/d	-0.10 (-2.43,2.32)	—								
Gel 1%, 50 mg/d	0.17 (-1.72,2.00)	0.27 (-2.76,3.22)	—							
Gel 1%, 75 mg/d	-0.63 (-2.35,1.10)	-0.54 (-3.46,2.37)	-0.80 (-3.33,1.74)	—						
Gel 1%, 100 mg/d	-0.38 (-1.71,0.65)	-0.28 (-3.12,2.20)	-0.55 (-2.87,1.55)	0.25 (-2.00,2.18)	—					
IM TU, 1000 mg/12 wk	-0.34 (-1.29,0.61)	-0.24 (-2.82,2.31)	-0.51 (-2.55,1.59)	0.29 (-1.67,2.22)	0.04 (-1.32,1.72)	—				
IM TE 125 mg/wk	0.69 (-1.02,2.42)	0.79 (-2.12,3.67)	0.52 (-1.97,3.10)	1.32 (-1.12,3.76)	1.07 (-0.87,3.31)	1.03 (-0.94,3.00)	—			
IM TE, 200 mg/2 wk	0.18 (-1.47,1.91)	0.28 (-1.38,1.92)	0.01 (-2.42,2.56)	0.82 (-1.58,3.20)	0.56 (-1.32,2.81)	0.53 (-1.38,2.51)	-0.51 (-2.88,1.91)	—		
IM TE, 300 mg/3 wk	-0.46 (-2.13,1.22)	-0.36 (-3.26,2.50)	-0.63 (-3.10,1.89)	0.17 (-2.22,2.53)	-0.08 (-1.95,2.12)	-0.12 (-2.05,1.81)	-1.15 (-3.54,1.29)	-0.64 (-3.02,1.67)	—	
IM Sustanon, 100 mg/2 wk†	-0.25 (-1.98,1.43)	-0.15 (-3.09,2.72)	-0.42 (-2.93,2.11)	0.38 (-2.11,2.79)	0.13 (-1.84,2.33)	0.09 (-1.92,2.06)	-0.94 (-3.39,1.45)	-0.44 (-2.87,1.92)	0.21 (-2.23,2.58)	—

Note: IM = intramuscular, TE = testosterone enanthate, TU = testosterone undecanoate.
*Random effects model. Analysis based on change from baseline. A negative SMD indicates improvement in depression. Significant changes are indicated by use of bold and colour (green indicates that the row treatment is significantly better than the column treatment, while red indicates that the row treatment is significantly worse than the column treatment). White indicates no significant difference between treatments.
†Blend of testosterone propionate, testosterone phenylpropionate, testosterone isocaproate, and testosterone decanoate.

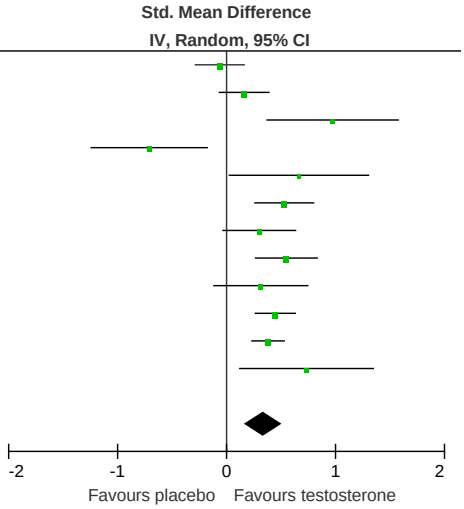
eFigure3: Individual trial results, libido

A) All trials

Study or Subgroup	Testosterone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Basaria 2015, p. 580	0.1	1.5	156	0.2	1.7	152	10.7%	-0.06 [-0.29, 0.16]	
Steidle 2003	0.7	1.3	307	0.5	1	99	10.6%	0.16 [-0.07, 0.39]	2003
Boyanov 2003	0.9	0.6	24	0.2	0.8	24	5.0%	0.97 [0.37, 1.57]	2003
Morales 2009	0.1	1.2	29	1	1.3	29	5.7%	-0.71 [-1.24, -0.18]	2009
Chiang 2009	1.4	1.8	20	0	2.3	20	4.6%	0.66 [0.03, 1.30]	2009
Jones 2011	1	1.4	108	0.2	1.6	112	9.9%	0.53 [0.26, 0.80]	2011
Spitzer 2012	0.7	2.6	70	0	2	70	8.7%	0.30 [-0.03, 0.63]	2012
Hackett 2013	0.5	1.4	97	-0.3	1.5	102	9.6%	0.55 [0.27, 0.83]	2013
Basaria 2015, p. 280	1.1	3.6	43	0.1	2.6	41	7.1%	0.31 [-0.12, 0.74]	2015
Snyder 2016	2.6	6.5	234	0	5	236	11.4%	0.45 [0.26, 0.63]	2016
Brock 2016	1.2	2.1	358	0.4	2.1	357	11.9%	0.38 [0.23, 0.53]	2016
Dhindsa 2016	1.2	1.1	22	0.3	1.3	22	4.8%	0.73 [0.12, 1.35]	2016
Total (95% CI)			**1468**			**1264**	**100.0%**	**0.33 [0.16, 0.50]**	

Heterogeneity: Tau² = 0.06; Chi² = 42.25, df = 11 (P < 0.0001); I² = 74%

Test for overall effect: Z = 3.85 (P = 0.0001)

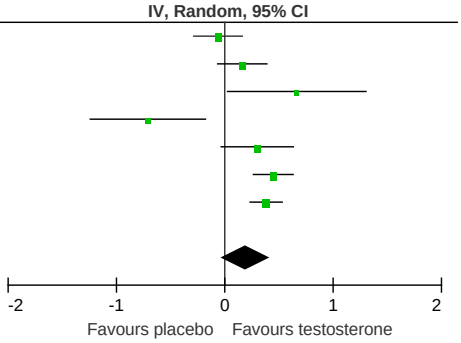


B) Trials involving men with no major comorbidities

Study or Subgroup	Testosterone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Basaria 2015, p. 580	0.1	1.5	156	0.2	1.7	152	16.7%	-0.06 [-0.29, 0.16]	
Steidle 2003	0.7	1.3	307	0.5	1	99	16.6%	0.16 [-0.07, 0.39]	2003
Chiang 2009	1.4	1.8	20	0	2.3	20	7.4%	0.66 [0.03, 1.30]	2009
Morales 2009	0.1	1.2	29	1	1.3	29	9.2%	-0.71 [-1.24, -0.18]	2009
Spitzer 2012	0.7	2.6	70	0	2	70	13.8%	0.30 [-0.03, 0.63]	2012
Snyder 2016	2.6	6.5	234	0	5	236	17.7%	0.45 [0.26, 0.63]	2016
Brock 2016	1.2	2.1	358	0.4	2.08	357	18.5%	0.38 [0.23, 0.53]	2016
Total (95% CI)			**1174**			**963**	**100.0%**	**0.19 [-0.03, 0.41]**	

Heterogeneity: Tau² = 0.06; Chi² = 29.74, df = 6 (P < 0.0001); I² = 80%

Test for overall effect: Z = 1.72 (P = 0.09)



eTable6: Libido – Bayesian network meta-analysis*

	Standardized mean difference (95% confidence interval)										
	Placebo	**Patch, 5 mg/d**	**Gel 1%, 50 mg/d**	**Gel 1%, 75 mg/d**	**Gel 1%, 100 mg/d**	**Gel 2%, 60 mg/d**	**Solution 2%, 60 mg/d**	**Oral TU, 120 mg/d**	**Oral, TU 160 mg/d**	**IM TU, 1000 mg/ 12 wk**	**IM TC, 250 mg/2wk**
Patch, 5 mg/d	0.17 (-0.13,0.46)	—									
Gel 1%, 50 mg/d	**0.32 (0.10,0.55)**	0.15 (-0.10,0.42)	—								
Gel 1%, 75 mg/d	-0.06 (-0.49,0.36)	-0.23 (-0.75,0.29)	-0.38 (-0.87,0.10)	—							
Gel 1%, 100 mg/d	**0.43 (0.16,0.69)**	**0.26 (0.00,0.52)**	0.11 (-0.14,0.35)	0.49 (-0.01,0.99)	—						
Gel 2%, 60 mg/d	**0.54 (0.09,0.99)**	0.37 (-0.17,0.91)	0.21 (-0.29,0.72)	0.60 (-0.01,1.22)	0.11 (-0.41,0.63)	—					
Solution 2%, 60 mg/d	0.39 (-0.01,0.79)	0.22 (-0.28,0.72)	0.07 (-0.39,0.53)	0.45 (-0.12,1.04)	-0.04 (-0.52,0.44)	-0.15 (-0.75,0.46)	—				
Oral TU, 120 mg/d	**1.00 (0.31,1.68)**	**0.83 (0.08,1.58)**	0.68 (-0.05,1.39)	**1.06 (0.25,1.87)**	0.57 (-0.17,1.30)	0.46 (-0.36,1.28)	0.61 (-0.18,1.39)	—			
Oral TU, 160 mg/d	**-0.72 (-1.35,-0.10)**	**-0.89 (-1.58,-0.19)**	**-1.04 (-1.70,-0.38)**	-0.66 (-1.41,0.10)	**-1.15 (-1.83,0.47)**	**-1.26 (-2.01,-0.49)**	**-1.11 (-1.84,-0.37)**	**-1.72 (-2.66,-0.78)**	—		
IM TU, 1000 mg/12 wk	**0.57 (0.11,1.03)**	0.40 (-0.14,0.95)	0.25 (-0.26,0.76)	**0.63 (0.00,1.26)**	0.14 (-0.38,0.67)	0.03 (-0.61,0.68)	0.18 (-0.42,0.79)	-0.43 (-1.25,0.41)	**1.29 (0.52,2.07)**	—	
IM TC, 250 mg/2wk	**0.71 (0.01,1.41)**	0.55 (-0.21,1.30)	0.39 (-0.34,1.12)	0.78 (-0.05,1.59)	0.29 (-0.46,1.04)	0.18 (-0.65,0.99)	0.33 (-0.47,1.13)	-0.28 (-1.25,0.72)	**1.44 (0.49,2.37)**	0.14 (-0.70,0.97)	—

Note: IM = intramuscular injection, TC = testostereon cypionate, TU = testosterone undecanoate.
*Random effects model. Analysis based on change from baseline. A positive SMD indicates improvement in libido. Significant changes are indicated by use of bold and colour (green indicates that the row treatment is significantly better than the column treatment, while red indicates that the row treatment is significantly worse than the column treatment). White indicates no significant difference between treatments.

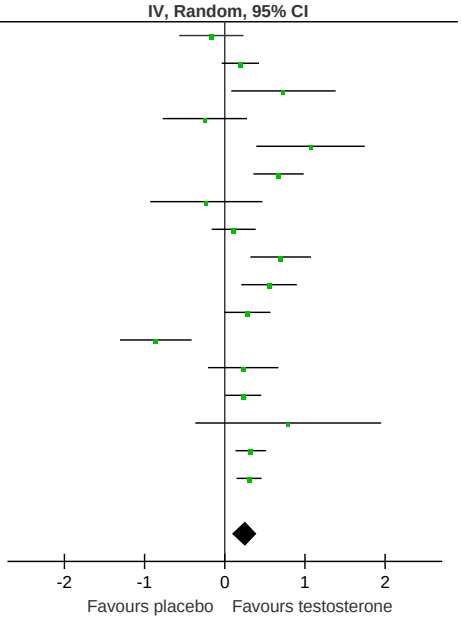
eFigure4: Individual trial results, erectile function

A) All trials

Study or Subgroup	Testosterone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Ng Tang Fui 2016	0	4.1	49	0.7	4.2	51	5.9%	-0.17 [-0.56, 0.23]	
Basaria 2015, p. 580	1.2	7.7	156	-0.4	8.7	152	7.8%	0.19 [-0.03, 0.42]	
Chiang 2007	5.8	5.8	20	1.2	6.5	20	3.6%	0.73 [0.09, 1.37]	2007
Morales 2009	-0.4	4.7	29	0.9	5.6	29	4.6%	-0.25 [-0.76, 0.27]	2009
Chiang 2009	7.3	7.8	20	-1.6	8.5	20	3.4%	1.07 [0.40, 1.74]	2009
Kalinchenko 2010	3.5	4.6	113	0.4	4.6	71	6.9%	0.67 [0.37, 0.98]	2010
Aversa 2010 p. 776	2.5	2	42	3	2.7	10	3.3%	-0.23 [-0.92, 0.46]	2010
Jones 2011	3.2	6	108	2.5	6.5	112	7.4%	0.11 [-0.15, 0.38]	2011
Ho 2011	2.3	4.8	60	-1	4.6	60	6.1%	0.70 [0.33, 1.07]	2011
Spitzer 2012	2	5.4	70	-1	5.4	70	6.5%	0.55 [0.21, 0.89]	2012
Hackett 2013	0.75	6.6	97	-1.1	6.5	102	7.2%	0.28 [0.00, 0.56]	2013
Gianatti 2014	-2	3.7	45	2	5.4	43	5.4%	-0.86 [-1.30, -0.42]	2014
Basaria 2015, p. 280	2.7	0.9	43	2.4	1.6	41	5.5%	0.23 [-0.20, 0.66]	2015
Konaka 2016	0.2	5.2	169	-1	5.2	165	7.9%	0.23 [0.02, 0.45]	2016
Chillaron 2016	5	7.5	6	0.5	2.1	7	1.5%	0.79 [-0.36, 1.94]	2016
Snyder 2016	3.1	6.9	234	1	6	236	8.3%	0.32 [0.14, 0.51]	2016
Brock 2016	3.4	8.89	358	0.7	8.88	357	8.6%	0.30 [0.16, 0.45]	2016
Total (95% CI)			**1619**			**1546**	**100.0%**	**0.25 [0.10, 0.41]**	

Heterogeneity: Tau² = 0.07; Chi² = 61.56, df = 16 (P < 0.00001); I² = 74%

Test for overall effect: Z = 3.19 (P = 0.001)

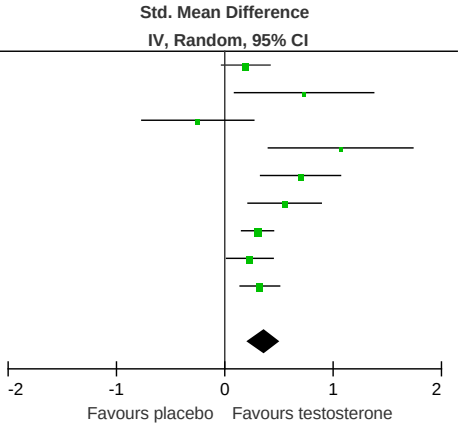


B) Trials involving men without major comorbidities

Study or Subgroup	Testosterone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Basaria 2015, p. 580	1.2	7.7	156	-0.4	8.7	152	15.0%	0.19 [-0.03, 0.42]	
Chiang 2007	5.8	5.8	20	1.2	6.5	20	4.3%	0.73 [0.09, 1.37]	2007
Morales 2009	-0.4	4.7	29	0.9	5.6	29	6.0%	-0.25 [-0.76, 0.27]	2009
Chiang 2009	7.3	7.8	20	-1.6	8.5	20	4.0%	1.07 [0.40, 1.74]	2009
Ho 2011	2.3	4.8	60	-1	4.57	60	9.4%	0.70 [0.33, 1.07]	2011
Spitzer 2012	2	5.4	70	-1	5.4	70	10.4%	0.55 [0.21, 0.89]	2012
Brock 2016	3.4	8.9	358	0.7	8.9	357	18.6%	0.30 [0.16, 0.45]	2016
Konaka 2016	0.2	5.15	169	-1	5.2	165	15.4%	0.23 [0.02, 0.45]	2016
Snyder 2016	3.1	6.9	234	1	6	236	16.9%	0.32 [0.14, 0.51]	2016
Total (95% CI)			**1116**			**1109**	**100.0%**	**0.36 [0.21, 0.51]**	

Heterogeneity: Tau² = 0.02; Chi² = 18.87, df = 8 (P = 0.02); I² = 58%

Test for overall effect: Z = 4.76 (P < 0.00001)



eTable7: Erectile function at end of treatment – Bayesian network meta-analysis*

	Standardized mean difference (95% confidence interval)									
	Placebo	Gel 1%, 50 mg/d	Gel 1%, 75 mg/d	Gel 1%, 100 mg/d	Gel 2%, 60 mg/d	Solution 2%, 60 mg/d	Oral, TU 160 mg/d	IM TU, 1000 mg/10 wk	IM TU, 1000 mg/12 wk	IM TE 250 mg/4wk
Gel 1%, 50 mg/d	0.65 (-0.11,1.42)	—								
Gel 1%, 75 mg/d	0.26 (-0.60,1.11)	-0.39 (-1.55,0.76)	—							
Gel 1%, 100 mg/d	0.55 (-0.70,1.80)	-0.10 (-1.57,1.35)	0.29 (-1.23,1.82)	—						
Gel 2%, 60 mg/d	0.11 (-1.11,1.33)	-0.54 (-1.99,0.90)	-0.15 (-1.66,1.34)	-0.44 (-2.18,1.31)	—					
Solution 2%, 60 mg/d	0.30 (-0.90,1.51)	-0.35 (-1.79,1.07)	0.04 (-1.43,1.53)	-0.25 (-1.99,1.50)	0.19 (-1.54,1.92)	—				
Oral TU, 160 mg/d	-0.47 (-1.41,0.43)	-1.12 (-2.34,0.05)	-0.73 (-2.02,0.51)	-1.03 (-2.60,0.52)	-0.59 (-2.14,0.95)	-0.78 (-2.31,0.73)	—			
IM TU, 1000 mg/10 wk	0.17 (-0.77,1.19)	-0.48 (-1.69,0.78)	-0.09 (-1.35,1.24)	-0.38 (-1.92,1.25)	0.06 (-1.47,1.66)	-0.13 (-1.63,1.46)	0.65 (-0.65,2.04)	—		
IM TU, 1000 mg/ 12 wk	0.21 (-0.36,0.76)	-0.44 (-1.40,0.49)	-0.05 (-1.10,0.96)	-0.34 (-1.72,1.02)	0.10 (-1.24,1.44)	-0.09 (-1.44,1.23)	0.68 (-0.29,1.68)	0.03 (-1.13,1.12)	—	
IM TE 250 mg/4wk	0.22 (-1.00,1.45)	-0.43 (-1.88,1.01)	-0.04 (-1.54,1.46)	-0.33 (-2.08,1.41)	0.11 (-1.63,1.84)	-0.08 (-1.80,1.62)	0.69 (-0.83,2.22)	0.04 (-1.57,1.57)	0.01 (-1.33,1.36)	—

Note: IM = intramuscular injection, TE = testosterone enanthate, TU = testosterone undecanoate.
*Random effects model. Analysis based on change from baseline. A positive SMD indicates improvement in erectile function. Significant changes are indicated by use of bold and colour (green indicates that the row treatment is significantly better than the column treatment, while red indicates that the row treatment is significantly worse than the column treatment). White indicates no significant difference between treatments.

eTable 8: Total testosterone level after 3 months of treatment – Bayesian network meta-analysis*

*Random effects model. Analysis based mean total testosterone level after treatment. A positive MD indicates a statistically significant improvement in total testosterone level. Significant changes are indicated by use of bold and colour (green indicates that the row treatment is significantly better than the column treatment, while red indicates that the row treatment is significantly worse than the column treatment). White indicates no significant difference between treatments.

Treatment	Reference	Mean difference (95% credible intervals)
Patch 4.8 mg/d	Placebo	12.46(-3.49,28.17)
Patch 5 mg/d		**5.06(0.88,9.25)**
Gel 1% 50 mg/d		**6.54(3.51,9.65)**
Gel 1% 75 mg/d		7.48(-2.02,17.01)
Gel 1% 100 mg/d		**9.82(6.19,13.44)**
Oral TU 120 mg/d		4.31(-4.08,12.69)
Oral TU 160 mg/d		3.64(-4.69,11.86)
Testosterone pellets 1200 mg		6.40(-5.08,17.89)
IM TU 1000 mg/12 wk		**8.91(2.80,15.08)**
IM TE 100 mg/wk		**12.12(3.48,20.83)**
IM TE 200 mg/2wk		6.26(-2.80,15.34)
IM TE 250 mg/3wk		**12.78(1.28,24.21)**
IM TC 200 mg/2 wk		3.25(-6.32,12.89)
IM TC 200 mg/4 wk		1.73(-8.61,12.15)
Durateston, IM, 250 mg/4wk		2.13(-8.21,12.60)
Patch 5 mg/d	Patch 4.8 mg/d	-7.40(-23.71,9.17)
Gel 1% 50 mg/d		-5.91(-21.92,10.35)
Gel 1% 75 mg/d		-4.98(-23.37,13.63)
Gel 1% 100 mg/d		-2.64(-18.80,13.74)
Oral TU 120 mg/d		-8.15(-26.04,9.82)
Oral TU 160 mg/d		-8.82(-22.30,4.67)
Testosterone pellets 1200 mg		-6.06(-18.69,6.69)
IM TU 1000 mg/12 wk		-3.55(-20.42,13.57)
IM TE 100 mg/wk		-0.34(-18.30,17.61)
IM TE 200 mg/2wk		-6.20(-24.42,12.21)
IM TE 250 mg/3wk		0.32(-10.51,11.25)
IM TC 200 mg/2 wk		-9.21(-27.76,9.46)
IM TC 200 mg/4 wk		-10.72(-29.59,8.36)
Durateston, IM, 250 mg/4wk		-10.33(-29.25,8.69)
Gel 1% 50 mg/d	Patch 5 mg/d	1.48(-2.69,5.71)
Gel 1% 75 mg/d		2.41(-7.90,12.76)
Gel 1% 100 mg/d		**4.76(0.40,9.04)**
Oral TU 120 mg/d		-0.75(-10.16,8.55)

Oral TU 160 mg/d		-1.43(-10.82,7.80)
Testosterone pellets 1200 mg		1.34(-10.92,13.53)
IM TU 1000 mg/12 wk		3.85(-3.58,11.27)
IM TE 100 mg/wk		7.06(-2.53,16.60)
IM TE 200 mg/2wk		1.19(-8.83,11.18)
IM TE 250 mg/3wk		7.72(-4.58,19.84)
IM TC 200 mg/2 wk		-1.81(-12.35,8.73)
IM TC 200 mg/4 wk		-3.33(-14.50,7.86)
Durateston, IM, 250 mg/4wk		-2.94(-14.12,8.32)
Gel 1% 75 mg/d	Gel 1% 50 mg/d	0.93(-8.98,10.93)
Gel 1% 100 mg/d		3.27(-0.68,7.16)
Oral TU 120 mg/d		-2.23(-11.30,6.62)
Oral TU 160 mg/d		-2.91(-11.82,5.84)
Testosterone pellets 1200 mg		-0.14(-12.11,11.71)
IM TU 1000 mg/12 wk		2.37(-4.49,9.22)
IM TE 100 mg/wk		5.57(-3.60,14.72)
IM TE 200 mg/2wk		-0.29(-9.83,9.28)
IM TE 250 mg/3wk		6.24(-5.72,18.05)
IM TC 200 mg/2 wk		-3.30(-13.42,6.78)
IM TC 200 mg/4 wk		-4.81(-15.66,5.96)
Durateston, IM, 250 mg/4wk		-4.42(-15.28,6.46)
Gel 1% 100 mg/d	Gel 1% 75 mg/d	2.34(-7.87,12.46)
Oral TU 120 mg/d		-3.17(-15.86,9.38)
Oral TU 160 mg/d		-3.84(-16.49,8.72)
Testosterone pellets 1200 mg		-1.07(-15.98,13.79)
IM TU 1000 mg/12 wk		1.44(-9.92,12.73)
IM TE 100 mg/wk		4.64(-8.23,17.49)
IM TE 200 mg/2wk		-1.22(-14.30,11.90)
IM TE 250 mg/3wk		5.31(-9.66,20.08)
IM TC 200 mg/2 wk		-4.23(-17.84,9.24)
IM TC 200 mg/4 wk		-5.74(-19.84,8.38)
Durateston, IM, 250 mg/4wk		-5.35(-19.41,8.93)
Oral TU 120 mg/d	Gel 1% 100 mg/d	-5.51(-14.69,3.57)
Oral TU 160 mg/d		-6.18(-15.23,2.79)
Testosterone pellets 1200 mg		-3.41(-15.41,8.57)
IM TU 1000 mg/12 wk		-0.91(-8.03,6.24)
IM TE 100 mg/wk		2.30(-7.08,11.64)
IM TE 200 mg/2wk		-3.56(-13.34,6.30)
IM TE 250 mg/3wk		2.96(-9.16,14.85)
IM TC 200 mg/2 wk		-6.57(-16.82,3.69)
IM TC 200 mg/4 wk		-8.08(-19.02,2.89)
Durateston, IM, 250 mg/4wk		-7.69(-18.61,3.38)

Oral TU 160 mg/d	Oral TU 120 mg/d	-0.67(-12.46,11.10)
Testosterone pellets 1200 mg		2.09(-12.01,16.29)
IM TU 1000 mg/12 wk		4.60(-5.79,14.94)
IM TE 100 mg/wk		7.81(-4.20,19.92)
IM TE 200 mg/2wk		1.95(-10.36,14.39)
IM TE 250 mg/3wk		8.47(-5.65,22.61)
IM TC 200 mg/2 wk		-1.06(-13.92,11.70)
IM TC 200 mg/4 wk		-2.58(-16.00,10.91)
Durateston, IM, 250 mg/4wk		-2.18(-15.61,11.22)
Testosterone pellets 1200 mg	Oral TU 160 mg/d	2.77(-5.26,10.82)
IM TU 1000 mg/12 wk		5.28(-5.00,15.64)
IM TE 100 mg/wk		8.48(-3.53,20.45)
IM TE 200 mg/2wk		2.62(-9.56,14.98)
IM TE 250 mg/3wk		**9.15(1.17,17.13)**
IM TC 200 mg/2 wk		-0.39(-13.19,12.34)
IM TC 200 mg/4 wk		-1.90(-15.18,11.34)
Durateston, IM, 250 mg/4wk		-1.51(-14.84,11.86)
IM TU 1000 mg/12 wk	Testosterone pellets 1200 mg	2.51(-10.54,15.55)
IM TE 100 mg/wk		5.71(-8.62,19.97)
IM TE 200 mg/2wk		-0.15(-14.76,14.51)
IM TE 250 mg/3wk		6.38(-0.25,13.01)
IM TC 200 mg/2 wk		-3.16(-18.21,11.86)
IM TC 200 mg/4 wk		-4.67(-20.16,10.75)
Durateston, IM, 250 mg/4wk		-4.28(-19.96,11.21)
IM TE 100 mg/wk	IM TU 1000 mg/12 wk	3.21(-7.33,13.81)
IM TE 200 mg/2wk		-2.66(-13.63,8.30)
IM TE 250 mg/3wk		3.87(-9.22,16.79)
IM TC 200 mg/2 wk		-5.66(-17.05,5.71)
IM TC 200 mg/4 wk		-7.18(-15.50,1.16)
Durateston, IM, 250 mg/4wk		-6.79(-15.25,1.65)
IM TE 200 mg/2wk	IM TE 100 mg/wk	-5.86(-18.36,6.71)
IM TE 250 mg/3wk		0.66(-13.63,15.00)
IM TC 200 mg/2 wk		-8.87(-21.88,4.14)
IM TC 200 mg/4 wk		-10.38(-23.84,3.13)
Durateston, IM, 250 mg/4wk		-9.99(-23.47,3.48)
IM TE 250 mg/3wk	IM TE 200 mg/2wk	6.53(-8.23,21.04)
IM TC 200 mg/2 wk		-3.01(-16.17,10.25)
IM TC 200 mg/4 wk		-4.52(-18.16,9.20)
Durateston, IM, 250 mg/4wk		-4.13(-17.94,9.72)
IM TC 200 mg/2 wk	IM TE 250 mg/3wk	-9.53(-24.53,5.59)
IM TC 200 mg/4 wk		-11.05(-26.44,4.43)
Durateston, IM, 250 mg/4wk		-10.65(-26.22,4.95)

IM TC 200 mg/4 wk	IM TC 200 mg/2 wk	-1.51(-15.53,12.52)
Durateston, IM, 250 mg/4wk		-1.12(-15.17,13.08)
Durateston, IM, 250 mg/4wk	IM TC 200 mg/4 wk	0.39(-8.03,8.79)

eTable 9: Total testosterone level after 6 months of treatment – Bayesian network meta-analysis*

*Random effects model. Analysis based mean total testosterone level after treatment. A positive MD indicates a statistically significant improvement in total testosterone level. Significant changes are indicated by use of bold and colour (green indicates that the row treatment is significantly better than the column treatment, while red indicates that the row treatment is significantly worse than the column treatment). White indicates no significant difference between treatments.

Treatment	Reference	Mean difference (95% credible interval)
Patch 4.8 mg/d	Placebo	10.69(-1.17,22.73)
Patch 5 mg/d		**8.45(0.51,16.35)**
Gel 1% 50 mg/d		**7.94(4.36,11.49)**
Gel 1% 75 mg/d		5.76(-0.75,12.29)
Gel 1% 100 mg/d		**7.47(3.50,11.40)**
Gel 2% 60 mg/d		**19.80(13.59,26.00)**
Gel 2.5%, 125 mg/d		**12.13(2.00,22.09)**
Gel (scrotal) 2.5%, 25 mg/d		7.89(-2.18,17.86)
Oral TU 120-160 mg/d		5.68(-0.52,11.88)
Oral TU 160 mg/d		1.84(-2.44,6.10)
Testosterone pellets 1200 mg		4.69(-2.86,12.17)
IM TU 1000 mg/12 wk		**8.07(3.71,12.46)**
IM TE 150 mg/2wk		**12.72(5.10,20.29)**
IM TE 200 mg/2wk		**10.10(2.68,17.61)**
IM TE 250 mg/3wk		**11.02(3.59,18.55)**
IM TE 300 mg/3wk		**18.25(10.92,25.60)**
IM TE 50-400 mg/1-2 wk		**14.74(4.55,25.01)**
IM TC 200 mg/2 wk		3.21(-4.73,11.12)
Patch 5 mg/d	Patch 4.8 mg/d	-2.24(-16.71,11.98)
Gel 1% 50 mg/d		-2.75(-15.42,9.56)
Gel 1% 75 mg/d		-4.94(-18.49,8.60)
Gel 1% 100 mg/d		-3.22(-15.94,9.31)
Gel 2% 60 mg/d		9.11(-4.41,22.45)
Gel 2.5%, 125 mg/d		1.44(-14.32,16.85)
Gel (scrotal) 2.5%, 25 mg/d		-2.80(-18.53,12.61)
Oral TU 120-160 mg/d		-5.01(-18.65,8.35)
Oral TU 160 mg/d		-8.85(-20.06,2.21)
Testosterone pellets 1200 mg		-6.01(-16.78,4.72)

IM TU 1000 mg/12 wk		-2.62(-14.99,9.53)
IM TE 150 mg/2wk		2.03(-12.24,16.16)
IM TE 200 mg/2wk		-0.59(-14.66,13.38)
IM TE 250 mg/3wk		0.33(-9.00,9.68)
IM TE 300 mg/3wk		7.56(-6.50,21.52)
IM TE 50-400 mg/1-2 wk		4.05(-11.55,19.64)
IM TC 200 mg/2 wk		-7.49(-21.86,6.80)
Gel 1% 50 mg/d	Patch 5 mg/d	-0.51(-9.17,8.26)
Gel 1% 75 mg/d		-2.70(-12.88,7.57)
Gel 1% 100 mg/d		-0.98(-9.71,7.83)
Gel 2% 60 mg/d		**11.35(1.38,21.45)**
Gel 2.5%, 125 mg/d		3.68(-2.57,9.89)
Gel (scrotal) 2.5%, 25 mg/d		-0.56(-6.82,5.64)
Oral TU 120-160 mg/d		-2.77(-12.83,7.29)
Oral TU 160 mg/d		-6.61(-15.60,2.37)
Testosterone pellets 1200 mg		-3.76(-14.64,7.17)
IM TU 1000 mg/12 wk		-0.38(-9.40,8.59)
IM TE 150 mg/2wk		4.27(-6.77,15.19)
IM TE 200 mg/2wk		1.65(-9.12,12.46)
IM TE 250 mg/3wk		2.57(-8.35,13.50)
IM TE 300 mg/3wk		9.80(-1.00,20.57)
IM TE 50-400 mg/1-2 wk		6.29(-6.46,19.33)
IM TC 200 mg/2 wk		-5.25(-16.35,5.95)
Gel 1% 75 mg/d	Gel 1% 50 mg/d	-2.19(-9.54,5.26)
Gel 1% 100 mg/d		-0.47(-5.79,4.89)
Gel 2% 60 mg/d		**11.86(4.68,19.05)**
Gel 2.5%, 125 mg/d		4.19(-6.52,14.80)
Gel (scrotal) 2.5%, 25 mg/d		-0.05(-10.72,10.61)
Oral TU 120-160 mg/d		-2.26(-9.34,4.96)
Oral TU 160 mg/d		**-6.10(-11.64,-0.46)**
Testosterone pellets 1200 mg		-3.25(-11.55,5.08)
IM TU 1000 mg/12 wk		0.13(-5.49,5.79)
IM TE 150 mg/2wk		4.78(-3.58,13.19)
IM TE 200 mg/2wk		2.16(-5.97,10.48)
IM TE 250 mg/3wk		3.08(-5.14,11.45)
IM TE 300 mg/3wk		**10.31(2.17,18.53)**
IM TE 50-400 mg/1-2 wk		6.80(-4.00,17.62)
IM TC 200 mg/2 wk		-4.74(-13.42,3.94)
Gel 1% 100 mg/d	Gel 1% 75 mg/d	1.71(-5.94,9.34)
Gel 2% 60 mg/d		**14.04(5.05,22.97)**
Gel 2.5%, 125 mg/d		6.37(-5.71,18.31)
Gel (scrotal) 2.5%, 25 mg/d		2.14(-9.89,14.03)

Oral TU 120-160 mg/d		-0.07(-9.16,8.90)
Oral TU 160 mg/d		-3.91(-11.78,3.88)
Testosterone pellets 1200 mg		-1.07(-10.98,8.82)
IM TU 1000 mg/12 wk		2.31(-5.63,10.19)
IM TE 150 mg/2wk		6.96(-3.13,17.01)
IM TE 200 mg/2wk		4.35(-5.60,14.23)
IM TE 250 mg/3wk		5.26(-4.59,15.19)
IM TE 300 mg/3wk		**12.50(2.64,22.31)**
IM TE 50-400 mg/1-2 wk		8.99(-3.00,21.03)
IM TC 200 mg/2 wk		-2.55(-12.74,7.68)
Gel 2% 60 mg/d	Gel 1% 100 mg/d	**12.33(5.03,19.71)**
Gel 2.5%, 125 mg/d		4.66(-6.17,15.34)
Gel (scrotal) 2.5%, 25 mg/d		0.42(-10.35,11.17)
Oral TU 120-160 mg/d		-1.79(-9.10,5.58)
Oral TU 160 mg/d		-5.63(-11.50,0.28)
Testosterone pellets 1200 mg		-2.78(-11.34,5.78)
IM TU 1000 mg/12 wk		0.60(-5.31,6.53)
IM TE 150 mg/2wk		5.25(-3.38,13.81)
IM TE 200 mg/2wk		2.63(-5.77,11.14)
IM TE 250 mg/3wk		3.55(-4.93,12.14)
IM TE 300 mg/3wk		**10.78(2.42,19.14)**
IM TE 50-400 mg/1-2 wk		7.28(-3.63,18.18)
IM TC 200 mg/2 wk		-4.27(-13.06,4.61)
Gel 2.5%, 125 mg/d	Gel 2% 60 mg/d	-7.67(-19.47,3.96)
Gel (scrotal) 2.5%, 25 mg/d		-11.91(-23.69,-0.16)
Oral TU 120-160 mg/d		-14.11(-22.91,-5.33)
Oral TU 160 mg/d		-17.96(-25.47,-10.36)
Testosterone pellets 1200 mg		-15.11(-24.85,-5.36)
IM TU 1000 mg/12 wk		-11.73(-19.31,-4.11)
IM TE 150 mg/2wk		-7.08(-16.88,2.74)
IM TE 200 mg/2wk		**-9.70(-19.39,-0.03)**
IM TE 250 mg/3wk		-8.78(-18.41,1.02)
IM TE 300 mg/3wk		-1.55(-11.11,8.12)
IM TE 50-400 mg/1-2 wk		-5.05(-16.93,6.87)
IM TC 200 mg/2 wk		**-16.59(-26.63,-6.52)**
Gel (scrotal) 2.5%, 25 mg/d	Gel 2.5%, 125 mg/d	-4.24(-10.53,1.98)
Oral TU 120-160 mg/d		-6.45(-18.26,5.33)
Oral TU 160 mg/d		-10.29(-21.22,0.66)
Testosterone pellets 1200 mg		-7.44(-19.87,5.14)
IM TU 1000 mg/12 wk		-4.06(-14.99,6.89)
IM TE 150 mg/2wk		0.59(-12.00,13.23)
IM TE 200 mg/2wk		-2.03(-14.56,10.54)

IM TE 250 mg/3wk		-1.11(-13.58,11.45)
IM TE 300 mg/3wk		6.12(-6.29,18.59)
IM TE 50-400 mg/1-2 wk		2.62(-11.57,17.04)
IM TC 200 mg/2 wk		-8.92(-21.55,3.89)
Oral TU 120-160 mg/d	Gel (scrotal) 2.5%, 25 mg/d	-2.21(-14.01,9.62)
Oral TU 160 mg/d		-6.05(-16.91,4.92)
Testosterone pellets 1200 mg		-3.21(-15.72,9.40)
IM TU 1000 mg/12 wk		0.18(-10.74,11.14)
IM TE 150 mg/2wk		4.82(-7.68,17.43)
IM TE 200 mg/2wk		2.21(-10.23,14.82)
IM TE 250 mg/3wk		3.13(-9.48,15.73)
IM TE 300 mg/3wk		10.36(-2.02,22.83)
IM TE 50-400 mg/1-2 wk		6.85(-7.36,21.24)
IM TC 200 mg/2 wk		-4.69(-17.36,8.11)
Oral TU 160 mg/d	Oral TU 120-160 mg/d	-3.84(-11.38,3.69)
Testosterone pellets 1200 mg		-1.00(-10.73,8.75)
IM TU 1000 mg/12 wk		2.39(-5.28,10.08)
IM TE 150 mg/2wk		7.03(-2.78,16.80)
IM TE 200 mg/2wk		4.42(-5.26,14.13)
IM TE 250 mg/3wk		5.33(-4.33,15.11)
IM TE 300 mg/3wk		**12.57(2.91,22.18)**
IM TE 50-400 mg/1-2 wk		9.06(-2.84,21.05)
IM TC 200 mg/2 wk		-2.48(-12.54,7.57)
Testosterone pellets 1200 mg	Oral TU 160 mg/d	2.84(-3.35,9.02)
IM TU 1000 mg/12 wk		**6.23(1.04,11.41)**
IM TE 150 mg/2wk		**10.87(2.16,19.57)**
IM TE 200 mg/2wk		8.26(-0.33,16.82)
IM TE 250 mg/3wk		**9.18(3.03,15.42)**
IM TE 300 mg/3wk		**16.41(7.93,25.00)**
IM TE 50-400 mg/1-2 wk		**12.90(1.81,23.95)**
IM TC 200 mg/2 wk		1.36(-7.75,10.40)
IM TU 1000 mg/12 wk	Testosterone pellets 1200 mg	3.38(-4.67,11.50)
IM TE 150 mg/2wk		8.03(-2.77,18.77)
IM TE 200 mg/2wk		5.42(-5.01,16.06)
IM TE 250 mg/3wk		**6.33(0.97,11.73)**
IM TE 300 mg/3wk		**13.57(3.19,24.08)**
IM TE 50-400 mg/1-2 wk		10.06(-2.53,22.73)
IM TC 200 mg/2 wk		-1.48(-12.38,9.46)
IM TE 150 mg/2wk	IM TU 1000 mg/12 wk	4.65(-4.13,13.37)
IM TE 200 mg/2wk		2.03(-6.70,10.69)
IM TE 250 mg/3wk		2.95(-5.08,11.11)
IM TE 300 mg/3wk		**10.18(1.58,18.75)**

IM TE 50-400 mg/1-2 wk		6.68(-4.45,17.75)
IM TC 200 mg/2 wk		-4.86(-13.89,4.19)
IM TE 200 mg/2wk	IM TE 150 mg/2wk	-2.61(-13.28,8.17)
IM TE 250 mg/3wk		-1.70(-12.39,9.20)
IM TE 300 mg/3wk		5.54(-5.10,16.15)
IM TE 50-400 mg/1-2 wk		2.03(-10.78,14.82)
IM TC 200 mg/2 wk		-9.51(-20.53,1.51)
IM TE 250 mg/3wk	IM TE 200 mg/2wk	0.92(-9.64,11.36)
IM TE 300 mg/3wk		8.15(-2.38,18.61)
IM TE 50-400 mg/1-2 wk		4.64(-7.93,17.27)
IM TC 200 mg/2 wk		-6.90(-17.80,4.00)
IM TE 300 mg/3wk	IM TE 250 mg/3wk	7.23(-3.23,17.75)
IM TE 50-400 mg/1-2 wk		3.73(-8.88,16.28)
IM TC 200 mg/2 wk	IM TE 300 mg/3wk	-7.81(-18.75,3.15)
IM TE 50-400 mg/1-2 wk		-3.51(-16.11,8.94)
IM TC 200 mg/2 wk		**-15.05(-25.92,-4.21)**
IM TC 200 mg/2 wk	IM TE 50-400 mg/1-2 wk	-11.54(-24.57,1.32)

eTable 10: Total testosterone levels at the end of treatment – Bayesian network meta-analysis*

*Random effects model. Analysis based mean total testosterone level after treatment. A positive MD indicates a statistically significant improvement in total testosterone level. Significant changes are indicated by use of bold and colour (green indicates that the row treatment is significantly better than the column treatment, while red indicates that the row treatment is significantly worse than the column treatment). White indicates no significant difference between treatments.

Treatment	Reference	Mean difference (95% credible interval)
Patch 4.8 mg/d	Placebo	8.00(-3.40,19.24)
Patch 5 mg/d		4.74(1.65,7.84)
Gel 1% 5 mg/d		3.66(-4.21,11.57)
Gel 1% 50 mg/d		6.54(4.27,8.85)
Gel 1% 75 mg/d		6.49(0.92,12.04)
Gel 1% 100 mg/d		9.76(6.92,12.61)
Gel 2% 60 mg/d		19.76(12.66,26.85)
Gel 2.5%, 125 mg/d		8.44(0.75,16.16)
Gel (scrotal) 2.5%, 25 mg/d		4.19(-3.53,11.91)
Solution 2%, 60 mg/d		8.47(0.47,16.40)
Oral TU 120 mg/d		4.32(-2.98,11.63)
Oral TU 160 mg/d		1.40(-2.28,5.08)
Oral TU 120-160 mg/d		5.69(-1.33,12.73)
Testosterone pellets 1200 mg		2.77(-3.99,9.50)
IM TU 1000 mg/9 wk		16.32(6.99,25.58)
IM TU 1000 mg/10 wk		5.70(0.07,11.29)

IM TU 1000 mg/12 wk		8.45(5.99,10.90)
IM TE 100 mg/wk		9.52(4.08,14.91)
IM TE 125 mg/wk		6.76(-3.38,16.87)
IM TE 150 mg/2wk		12.71(4.36,21.09)
IM TE 200 mg/2wk		10.67(5.96,15.35)
IM TE 250 mg/3wk		8.33(2.98,13.71)
IM TE 300 mg/3wk		18.26(9.96,26.49)
IM TE 50-400 mg/1-2 wk		14.74(3.91,25.46)
IM TC 200 mg/2 wk		3.20(-5.49,11.85)
IM TC 200 mg/4 wk		1.30(-6.39,8.98)
IM TC 250 mg/2wk		9.73(1.91,17.51)
Durateston, IM, 250 mg/4wk		1.67(-6.17,9.42)
Patch 5 mg/d	Patch 4.8 mg/d	-3.26(-14.89,8.56)
Gel 1% 5 mg/d		-4.34(-18.04,9.54)
Gel 1% 50 mg/d		-1.46(-12.93,10.15)
Gel 1% 75 mg/d		-1.51(-14.10,11.24)
Gel 1% 100 mg/d		1.76(-9.83,13.46)
Gel 2% 60 mg/d		11.76(-1.57,25.26)
Gel 2.5%, 125 mg/d		0.44(-13.20,14.18)
Gel (scrotal) 2.5%, 25 mg/d		-3.81(-17.47,9.95)
Solution 2%, 60 mg/d		0.47(-13.38,14.35)
Oral TU 120 mg/d		-3.68(-17.02,9.84)
Oral TU 160 mg/d		-6.60(-17.82,4.81)
Oral TU 120-160 mg/d		-2.31(-15.69,11.06)
Testosterone pellets 1200 mg		-5.23(-16.69,6.32)
IM TU 1000 mg/9 wk		8.32(-4.22,20.91)
IM TU 1000 mg/10 wk		-2.30(-14.89,10.43)
IM TU 1000 mg/12 wk		0.45(-11.02,12.05)
IM TE 100 mg/wk		1.52(-10.96,14.13)
IM TE 125 mg/wk		-1.24(-16.45,13.89)
IM TE 150 mg/2wk		4.71(-9.35,18.84)
IM TE 200 mg/2wk		2.67(-9.60,14.94)
IM TE 250 mg/3wk		0.33(-9.63,10.45)
IM TE 300 mg/3wk		10.26(-3.79,24.37)
IM TE 50-400 mg/1-2 wk		6.75(-8.90,22.49)
IM TC 200 mg/2 wk		-4.80(-19.10,9.52)
IM TC 200 mg/4 wk		-6.70(-20.28,7.08)
IM TC 250 mg/2wk		1.73(-11.91,15.43)
Durateston, IM, 250 mg/4wk		-6.33(-20.01,7.57)
Gel 1% 5 mg/d	Patch 5 mg/d	-1.08(-9.49,7.42)
Gel 1% 50 mg/d		1.80(-1.49,5.16)
Gel 1% 75 mg/d		1.76(-4.64,8.14)

Gel 1% 100 mg/d		5.02(1.52,8.49)
Gel 2% 60 mg/d		15.02(7.19,22.80)
Gel 2.5%, 125 mg/d		3.70(-3.39,10.73)
Gel (scrotal) 2.5%, 25 mg/d		-0.55(-7.68,6.53)
Solution 2%, 60 mg/d		3.73(-4.85,12.32)
Oral TU 120 mg/d		-0.41(-8.32,7.44)
Oral TU 160 mg/d		-3.33(-8.17,1.43)
Oral TU 120-160 mg/d		0.95(-6.78,8.61)
Testosterone pellets 1200 mg		-1.97(-9.42,5.39)
IM TU 1000 mg/9 wk		11.58(1.73,21.42)
IM TU 1000 mg/10 wk		0.96(-5.42,7.38)
IM TU 1000 mg/12 wk		3.72(-0.31,7.66)
IM TE 100 mg/wk		4.78(-1.44,10.97)
IM TE 125 mg/wk		2.02(-8.51,12.56)
IM TE 150 mg/2wk		7.97(-0.95,16.86)
IM TE 200 mg/2wk		5.93(0.94,10.87)
IM TE 250 mg/3wk		3.59(-2.64,9.81)
IM TE 300 mg/3wk		13.52(4.66,22.31)
IM TE 50-400 mg/1-2 wk		10.01(-1.36,21.18)
IM TC 200 mg/2 wk		-1.54(-10.74,7.65)
IM TC 200 mg/4 wk		-3.44(-11.77,4.80)
IM TC 250 mg/2wk		4.99(-3.43,13.41)
Durateston, IM, 250 mg/4wk		-3.07(-11.56,5.28)
Gel 1% 50 mg/d	Gel 1% 5 mg/d	2.88(-5.34,11.08)
Gel 1% 75 mg/d		2.83(-6.84,12.54)
Gel 1% 100 mg/d		6.10(-2.30,14.48)
Gel 2% 60 mg/d		16.10(5.47,26.65)
Gel 2.5%, 125 mg/d		4.78(-6.22,15.83)
Gel (scrotal) 2.5%, 25 mg/d		0.53(-10.48,11.48)
Solution 2%, 60 mg/d		4.81(-6.33,15.99)
Oral TU 120 mg/d		0.66(-9.98,11.41)
Oral TU 160 mg/d		-2.26(-10.97,6.42)
Oral TU 120-160 mg/d		2.02(-8.54,12.63)
Testosterone pellets 1200 mg		-0.89(-11.28,9.45)
IM TU 1000 mg/9 wk		12.66(0.32,24.84)
IM TU 1000 mg/10 wk		2.04(-7.64,11.75)
IM TU 1000 mg/12 wk		4.79(-3.47,12.95)
IM TE 100 mg/wk		5.86(-3.72,15.40)
IM TE 125 mg/wk		3.10(-9.72,15.94)
IM TE 150 mg/2wk		9.05(-2.41,20.56)
IM TE 200 mg/2wk		7.01(-2.27,16.13)
IM TE 250 mg/3wk		4.67(-4.87,14.18)

IM TE 300 mg/3wk		14.60(3.17,26.00)
IM TE 50-400 mg/1-2 wk		11.08(-2.35,24.44)
IM TC 200 mg/2 wk		-0.46(-12.22,11.21)
IM TC 200 mg/4 wk		-2.37(-13.33,8.57)
IM TC 250 mg/2wk		6.07(-5.05,17.18)
Durateston, IM, 250 mg/4wk		-1.99(-13.08,9.06)
Gel 1% 75 mg/d	Gel 1% 50 mg/d	-0.05(-6.06,5.96)
Gel 1% 100 mg/d		3.22(0.05,6.36)
Gel 2% 60 mg/d		13.22(5.72,20.65)
Gel 2.5%, 125 mg/d		1.90(-5.89,9.68)
Gel (scrotal) 2.5%, 25 mg/d		-2.35(-10.23,5.47)
Solution 2%, 60 mg/d		1.93(-6.45,10.21)
Oral TU 120 mg/d		-2.22(-9.89,5.36)
Oral TU 160 mg/d		-5.14(-9.50,-0.83)
Oral TU 120-160 mg/d		-0.86(-8.26,6.53)
Testosterone pellets 1200 mg		-3.77(-10.93,3.32)
IM TU 1000 mg/9 wk		9.78(0.12,19.31)
IM TU 1000 mg/10 wk		-0.84(-6.93,5.22)
IM TU 1000 mg/12 wk		1.91(-1.49,5.22)
IM TE 100 mg/wk		2.98(-2.97,8.82)
IM TE 125 mg/wk		0.22(-10.17,10.56)
IM TE 150 mg/2wk		6.17(-2.50,14.84)
IM TE 200 mg/2wk		4.13(-0.98,9.17)
IM TE 250 mg/3wk		1.79(-4.11,7.62)
IM TE 300 mg/3wk		11.72(3.13,20.20)
IM TE 50-400 mg/1-2 wk		8.20(-2.93,19.12)
IM TC 200 mg/2 wk		-3.34(-12.34,5.62)
IM TC 200 mg/4 wk		-5.25(-13.24,2.71)
IM TC 250 mg/2wk		3.19(-4.96,11.30)
Durateston, IM, 250 mg/4wk		-4.87(-13.08,3.23)
Gel 1% 100 mg/d	Gel 1% 75 mg/d	3.26(-3.00,9.49)
Gel 2% 60 mg/d		13.27(4.21,22.29)
Gel 2.5%, 125 mg/d		1.95(-7.52,11.42)
Gel (scrotal) 2.5%, 25 mg/d		-2.30(-11.80,7.19)
Solution 2%, 60 mg/d		1.98(-7.79,11.68)
Oral TU 120 mg/d		-2.17(-11.46,7.10)
Oral TU 160 mg/d		-5.09(-11.81,1.62)
Oral TU 120-160 mg/d		-0.81(-9.76,8.21)
Testosterone pellets 1200 mg		-3.72(-12.49,5.06)
IM TU 1000 mg/9 wk		9.83(-1.12,20.61)
IM TU 1000 mg/10 wk		-0.79(-8.71,7.09)
IM TU 1000 mg/12 wk		1.96(-4.14,8.02)

IM TE 100 mg/wk		3.03(-4.78,10.84)
IM TE 125 mg/wk		0.27(-11.29,11.76)
IM TE 150 mg/2wk		6.21(-3.81,16.26)
IM TE 200 mg/2wk		4.18(-3.13,11.49)
IM TE 250 mg/3wk		1.84(-5.91,9.60)
IM TE 300 mg/3wk		11.76(1.77,21.71)
IM TE 50-400 mg/1-2 wk		8.25(-3.95,20.40)
IM TC 200 mg/2 wk		-3.30(-13.57,7.03)
IM TC 200 mg/4 wk		-5.20(-14.75,4.38)
IM TC 250 mg/2wk		3.24(-6.31,12.84)
Durateston, IM, 250 mg/4wk		-4.82(-14.54,4.73)
Gel 2% 60 mg/d	Gel 1% 100 mg/d	10.00(2.31,17.65)
Gel 2.5%, 125 mg/d		-1.32(-9.14,6.53)
Gel (scrotal) 2.5%, 25 mg/d		-5.57(-13.46,2.30)
Solution 2%, 60 mg/d		-1.29(-9.81,7.12)
Oral TU 120 mg/d		-5.43(-13.31,2.41)
Oral TU 160 mg/d		-8.35(-13.01,-3.72)
Oral TU 120-160 mg/d		-4.07(-11.66,3.46)
Testosterone pellets 1200 mg		-6.98(-14.31,0.32)
IM TU 1000 mg/9 wk		6.56(-3.21,16.30)
IM TU 1000 mg/10 wk		-4.05(-10.36,2.25)
IM TU 1000 mg/12 wk		-1.30(-5.08,2.39)
IM TE 100 mg/wk		-0.24(-6.33,5.86)
IM TE 125 mg/wk		-3.00(-13.56,7.45)
IM TE 150 mg/2wk		2.95(-5.87,11.76)
IM TE 200 mg/2wk		0.91(-4.37,6.24)
IM TE 250 mg/3wk		-1.43(-7.51,4.70)
IM TE 300 mg/3wk		8.50(-0.26,17.19)
IM TE 50-400 mg/1-2 wk		4.99(-6.29,16.05)
IM TC 200 mg/2 wk		-6.56(-15.67,2.62)
IM TC 200 mg/4 wk		-8.46(-16.58,-0.35)
IM TC 250 mg/2wk		-0.03(-8.32,8.21)
Durateston, IM, 250 mg/4wk		-8.09(-16.37,0.19)
Gel 2.5%, 125 mg/d	Gel 2% 60 mg/d	-11.32(-21.81,-0.76)
Gel (scrotal) 2.5%, 25 mg/d		-15.57(-26.01,-5.14)
Solution 2%, 60 mg/d		-11.29(-22.04,-0.61)
Oral TU 120 mg/d		-15.44(-25.55,-5.26)
Oral TU 160 mg/d		-18.36(-26.38,-10.40)
Oral TU 120-160 mg/d		-14.08(-24.01,-4.07)
Testosterone pellets 1200 mg		-16.99(-26.76,-7.21)
IM TU 1000 mg/9 wk		-3.44(-15.22,8.28)
IM TU 1000 mg/10 wk		-14.06(-23.21,-4.99)

IM TU 1000 mg/12 wk		-11.31(-18.81,-3.79)
IM TE 100 mg/wk		-10.24(-19.18,-1.26)
IM TE 125 mg/wk		-13.00(-25.43,-0.67)
IM TE 150 mg/2wk		-7.05(-18.02,3.89)
IM TE 200 mg/2wk		-9.09(-17.56,-0.59)
IM TE 250 mg/3wk		-11.43(-20.28,-2.55)
IM TE 300 mg/3wk		-1.50(-12.41,9.29)
IM TE 50-400 mg/1-2 wk		-5.02(-17.95,7.94)
IM TC 200 mg/2 wk		-16.56(-27.65,-5.38)
IM TC 200 mg/4 wk		-18.47(-28.79,-7.99)
IM TC 250 mg/2wk		-10.03(-20.60,0.55)
Durateston, IM, 250 mg/4wk		-18.09(-28.55,-7.51)
Gel (scrotal) 2.5%, 25 mg/d	Gel 2.5%, 125 mg/d	-4.25(-11.32,2.85)
Solution 2%, 60 mg/d		0.03(-11.01,11.05)
Oral TU 120 mg/d		-4.11(-14.77,6.43)
Oral TU 160 mg/d		-7.03(-15.56,1.49)
Oral TU 120-160 mg/d		-2.75(-13.20,7.62)
Testosterone pellets 1200 mg		-5.67(-15.93,4.50)
IM TU 1000 mg/9 wk		7.88(-4.23,19.98)
IM TU 1000 mg/10 wk		-2.74(-12.35,6.74)
IM TU 1000 mg/12 wk		0.02(-8.05,8.09)
IM TE 100 mg/wk		1.08(-8.38,10.49)
IM TE 125 mg/wk		-1.68(-14.40,11.04)
IM TE 150 mg/2wk		4.27(-7.05,15.61)
IM TE 200 mg/2wk		2.23(-6.41,10.86)
IM TE 250 mg/3wk		-0.11(-9.59,9.27)
IM TE 300 mg/3wk		9.82(-1.46,21.10)
IM TE 50-400 mg/1-2 wk		6.31(-7.08,19.61)
IM TC 200 mg/2 wk		-5.24(-16.86,6.39)
IM TC 200 mg/4 wk		-7.14(-18.05,3.70)
IM TC 250 mg/2wk		1.29(-9.68,12.14)
Durateston, IM, 250 mg/4wk		-6.77(-17.77,4.17)
Solution 2%, 60 mg/d	Gel (scrotal) 2.5%, 25 mg/d	4.28(-6.76,15.29)
Oral TU 120 mg/d		0.13(-10.41,10.69)
Oral TU 160 mg/d		-2.79(-11.32,5.78)
Oral TU 120-160 mg/d		1.49(-8.95,11.85)
Testosterone pellets 1200 mg		-1.42(-11.69,8.77)
IM TU 1000 mg/9 wk		12.13(-0.05,24.28)
IM TU 1000 mg/10 wk		1.51(-8.10,11.01)
IM TU 1000 mg/12 wk		4.26(-3.85,12.36)
IM TE 100 mg/wk		5.33(-4.13,14.73)
IM TE 125 mg/wk		2.57(-10.20,15.23)

IM TE 150 mg/2wk		8.52(-2.86,19.92)
IM TE 200 mg/2wk		6.48(-2.21,15.12)
IM TE 250 mg/3wk		4.14(-5.23,13.54)
IM TE 300 mg/3wk		14.07(2.81,25.31)
IM TE 50-400 mg/1-2 wk		10.55(-2.91,23.84)
IM TC 200 mg/2 wk		-0.99(-12.60,10.58)
IM TC 200 mg/4 wk		-2.90(-13.82,8.03)
IM TC 250 mg/2wk		5.54(-5.44,16.60)
Durateston, IM, 250 mg/4wk		-2.52(-13.52,8.43)
Oral TU 120 mg/d	Solution 2%, 60 mg/d	-4.15(-14.97,6.71)
Oral TU 160 mg/d		-7.07(-15.82,1.75)
Oral TU 120-160 mg/d		-2.79(-13.42,7.91)
Testosterone pellets 1200 mg		-5.70(-16.19,4.77)
IM TU 1000 mg/9 wk		7.85(-4.39,20.17)
IM TU 1000 mg/10 wk		-2.77(-12.56,7.00)
IM TU 1000 mg/12 wk		-0.02(-8.34,8.36)
IM TE 100 mg/wk		1.05(-8.64,10.74)
IM TE 125 mg/wk		-1.71(-14.70,11.26)
IM TE 150 mg/2wk		4.24(-7.33,15.76)
IM TE 200 mg/2wk		2.20(-6.98,11.47)
IM TE 250 mg/3wk		-0.14(-9.75,9.50)
IM TE 300 mg/3wk		9.79(-1.75,21.38)
IM TE 50-400 mg/1-2 wk		6.27(-7.18,19.70)
IM TC 200 mg/2 wk		-5.27(-17.13,6.58)
IM TC 200 mg/4 wk		-7.17(-18.19,4.01)
IM TC 250 mg/2wk		1.26(-9.92,12.47)
Durateston, IM, 250 mg/4wk		-6.80(-17.95,4.39)
Oral TU 160 mg/d	Oral TU 120 mg/d	-2.92(-11.18,5.30)
Oral TU 120-160 mg/d		1.36(-8.75,11.51)
Testosterone pellets 1200 mg		-1.55(-11.47,8.35)
IM TU 1000 mg/9 wk		11.99(0.22,23.80)
IM TU 1000 mg/10 wk		1.38(-7.80,10.65)
IM TU 1000 mg/12 wk		4.13(-3.60,11.79)
IM TE 100 mg/wk		5.20(-3.98,14.29)
IM TE 125 mg/wk		2.44(-10.06,15.00)
IM TE 150 mg/2wk		8.38(-2.65,19.47)
IM TE 200 mg/2wk		6.35(-2.24,15.06)
IM TE 250 mg/3wk		4.01(-5.04,13.13)
IM TE 300 mg/3wk		13.93(2.85,24.90)
IM TE 50-400 mg/1-2 wk		10.42(-2.47,23.36)
IM TC 200 mg/2 wk		-1.13(-12.50,10.16)
IM TC 200 mg/4 wk		-3.03(-13.54,7.52)

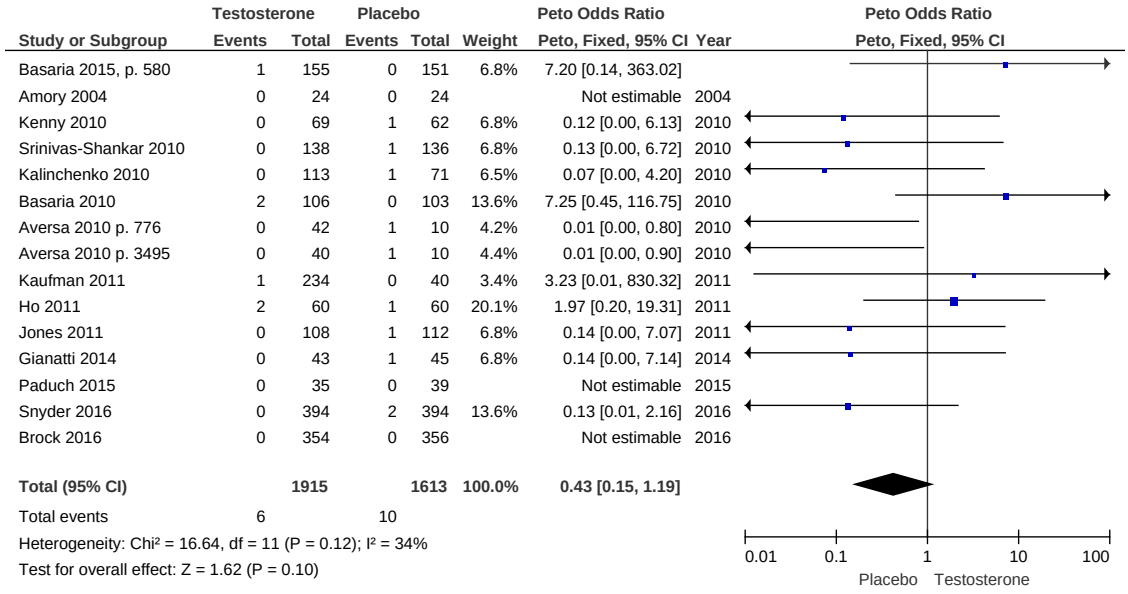
IM TC 250 mg/2wk		5.41(-5.24,16.03)
Durateston, IM, 250 mg/4wk		-2.65(-13.24,7.90)
Oral TU 120-160 mg/d	Oral TU 160 mg/d	4.28(-3.65,12.24)
Testosterone pellets 1200 mg		1.37(-5.02,7.65)
IM TU 1000 mg/9 wk		14.91(5.60,24.22)
IM TU 1000 mg/10 wk		4.30(-2.44,10.98)
IM TU 1000 mg/12 wk		7.05(2.88,11.22)
IM TE 100 mg/wk		8.12(1.58,14.65)
IM TE 125 mg/wk		5.36(-5.44,16.14)
IM TE 150 mg/2wk		11.30(2.17,20.50)
IM TE 200 mg/2wk		9.27(3.31,15.24)
IM TE 250 mg/3wk		6.93(1.62,12.24)
IM TE 300 mg/3wk		16.85(7.78,25.85)
IM TE 50-400 mg/1-2 wk		13.34(1.90,24.69)
IM TC 200 mg/2 wk		1.79(-7.65,11.19)
IM TC 200 mg/4 wk		-0.11(-8.45,8.32)
IM TC 250 mg/2wk		8.33(-0.32,16.90)
Durateston, IM, 250 mg/4wk		0.27(-8.25,8.73)
Testosterone pellets 1200 mg	Oral TU 120-160 mg/d	-2.91(-12.66,6.81)
IM TU 1000 mg/9 wk		10.63(-1.05,22.19)
IM TU 1000 mg/10 wk		0.02(-8.97,9.02)
IM TU 1000 mg/12 wk		2.77(-4.70,10.19)
IM TE 100 mg/wk		3.83(-5.07,12.72)
IM TE 125 mg/wk		1.08(-11.31,13.34)
IM TE 150 mg/2wk		7.02(-3.93,18.04)
IM TE 200 mg/2wk		4.99(-3.53,13.53)
IM TE 250 mg/3wk		2.65(-6.16,11.47)
IM TE 300 mg/3wk		12.57(1.68,23.38)
IM TE 50-400 mg/1-2 wk		9.06(-3.94,21.88)
IM TC 200 mg/2 wk		-2.49(-13.64,8.66)
IM TC 200 mg/4 wk		-4.39(-14.76,6.03)
IM TC 250 mg/2wk		4.05(-6.43,14.57)
Durateston, IM, 250 mg/4wk		-4.02(-14.52,6.43)
IM TU 1000 mg/9 wk	Testosterone pellets 1200 mg	13.55(3.98,23.17)
IM TU 1000 mg/10 wk		2.93(-5.76,11.79)
IM TU 1000 mg/12 wk		5.68(-1.39,12.77)
IM TE 100 mg/wk		6.75(-1.86,15.41)
IM TE 125 mg/wk		3.99(-8.13,16.03)
IM TE 150 mg/2wk		9.93(-0.73,20.72)
IM TE 200 mg/2wk		7.90(-0.28,16.12)
IM TE 250 mg/3wk		5.56(-0.16,11.31)
IM TE 300 mg/3wk		15.48(4.84,26.11)

IM TE 50-400 mg/1-2 wk		11.97(-0.87,24.56)
IM TC 200 mg/2 wk		0.43(-10.60,11.33)
IM TC 200 mg/4 wk		-1.48(-11.65,8.68)
IM TC 250 mg/2wk		6.96(-3.27,17.22)
Durateston, IM, 250 mg/4wk		-1.10(-11.31,9.12)
IM TU 1000 mg/10 wk	IM TU 1000 mg/9 wk	-10.62(-21.47,0.34)
IM TU 1000 mg/12 wk		-7.87(-17.42,1.71)
IM TE 100 mg/wk		-6.80(-17.58,3.97)
IM TE 125 mg/wk		-9.56(-23.43,4.23)
IM TE 150 mg/2wk		-3.61(-16.13,8.87)
IM TE 200 mg/2wk		-5.65(-16.09,4.77)
IM TE 250 mg/3wk		-7.99(-15.63,-0.43)
IM TE 300 mg/3wk		1.94(-10.58,14.38)
IM TE 50-400 mg/1-2 wk		-1.57(-15.93,12.57)
IM TC 200 mg/2 wk		-13.12(-25.76,-0.50)
IM TC 200 mg/4 wk		-15.02(-27.02,-2.97)
IM TC 250 mg/2wk		-6.59(-18.64,5.51)
Durateston, IM, 250 mg/4wk		-14.65(-26.65,-2.55)
IM TU 1000 mg/12 wk	IM TU 1000 mg/10 wk	2.75(-3.39,8.87)
IM TE 100 mg/wk		3.82(-4.02,11.63)
IM TE 125 mg/wk		1.06(-10.55,12.59)
IM TE 150 mg/2wk		7.00(-3.13,17.12)
IM TE 200 mg/2wk		4.97(-2.38,12.33)
IM TE 250 mg/3wk		2.63(-5.20,10.43)
IM TE 300 mg/3wk		12.55(2.61,22.50)
IM TE 50-400 mg/1-2 wk		9.04(-3.15,21.15)
IM TC 200 mg/2 wk		-2.51(-12.86,7.88)
IM TC 200 mg/4 wk		-4.41(-13.89,5.12)
IM TC 250 mg/2wk		4.03(-5.67,13.61)
Durateston, IM, 250 mg/4wk		-4.03(-13.63,5.52)
IM TE 100 mg/wk	IM TU 1000 mg/12 wk	1.07(-4.91,7.00)
IM TE 125 mg/wk		-1.69(-12.18,8.70)
IM TE 150 mg/2wk		4.25(-4.40,13.04)
IM TE 200 mg/2wk		2.22(-3.10,7.50)
IM TE 250 mg/3wk		-0.12(-5.92,5.72)
IM TE 300 mg/3wk		9.80(1.20,18.32)
IM TE 50-400 mg/1-2 wk		6.29(-4.89,17.26)
IM TC 200 mg/2 wk		-5.26(-14.26,3.76)
IM TC 200 mg/4 wk		-7.16(-14.34,0.12)
IM TC 250 mg/2wk		1.28(-6.89,9.44)
Durateston, IM, 250 mg/4wk		-6.78(-14.19,0.56)
IM TE 125 mg/wk	IM TE 100 mg/wk	-2.76(-14.21,8.71)

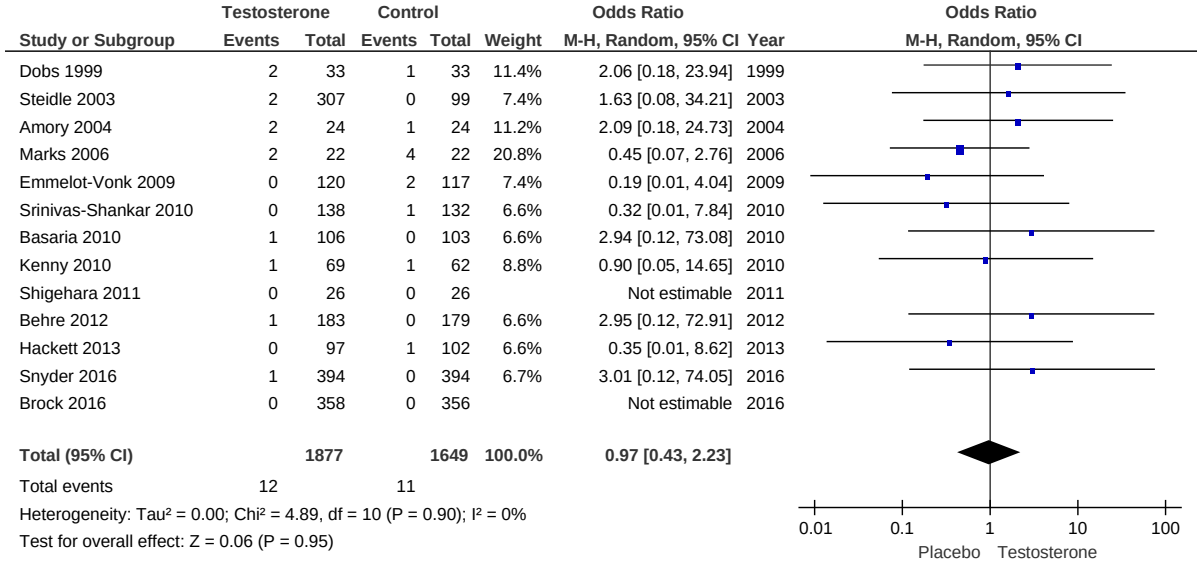
IM TE 150 mg/2wk		3.19(-6.80,13.17)
IM TE 200 mg/2wk		1.15(-6.03,8.28)
IM TE 250 mg/3wk		-1.19(-8.76,6.47)
IM TE 300 mg/3wk		8.74(-1.14,18.58)
IM TE 50-400 mg/1-2 wk		5.22(-6.94,17.26)
IM TC 200 mg/2 wk		-6.32(-16.59,3.99)
IM TC 200 mg/4 wk		-8.22(-17.53,1.14)
IM TC 250 mg/2wk		0.21(-9.33,9.74)
Durateston, IM, 250 mg/4wk		-7.85(-17.40,1.61)
IM TE 150 mg/2wk	IM TE 125 mg/wk	5.95(-7.16,19.13)
IM TE 200 mg/2wk		3.91(-7.29,15.04)
IM TE 250 mg/3wk		1.57(-9.82,13.12)
IM TE 300 mg/3wk		11.50(-1.54,24.55)
IM TE 50-400 mg/1-2 wk		7.98(-6.80,22.76)
IM TC 200 mg/2 wk		-3.56(-16.94,9.75)
IM TC 200 mg/4 wk		-5.47(-18.14,7.27)
IM TC 250 mg/2wk		2.97(-9.79,15.85)
Durateston, IM, 250 mg/4wk		-5.09(-17.80,7.77)
IM TE 200 mg/2wk	IM TE 150 mg/2wk	-2.04(-11.66,7.57)
IM TE 250 mg/3wk		-4.38(-14.31,5.56)
IM TE 300 mg/3wk		5.55(-6.15,17.34)
IM TE 50-400 mg/1-2 wk		2.04(-11.74,15.72)
IM TC 200 mg/2 wk		-9.51(-21.66,2.54)
IM TC 200 mg/4 wk		-11.41(-22.70,0.00)
IM TC 250 mg/2wk		-2.98(-14.42,8.45)
Durateston, IM, 250 mg/4wk		-11.04(-22.52,0.42)
IM TE 250 mg/3wk	IM TE 200 mg/2wk	-2.34(-9.48,4.87)
IM TE 300 mg/3wk		7.59(-1.89,17.04)
IM TE 50-400 mg/1-2 wk		4.07(-7.82,15.86)
IM TC 200 mg/2 wk		-7.47(-17.31,2.38)
IM TC 200 mg/4 wk		-9.37(-18.42,-0.35)
IM TC 250 mg/2wk		-0.94(-9.99,8.19)
Durateston, IM, 250 mg/4wk		-9.00(-18.14,0.03)
IM TE 300 mg/3wk	IM TE 250 mg/3wk	9.93(0.08,19.73)
IM TE 50-400 mg/1-2 wk		6.41(-5.72,18.40)
IM TC 200 mg/2 wk		-5.13(-15.34,5.05)
IM TC 200 mg/4 wk		-7.04(-16.28,2.31)
IM TC 250 mg/2wk		1.40(-8.03,10.77)
Durateston, IM, 250 mg/4wk		-6.66(-16.10,2.75)
IM TE 50-400 mg/1-2 wk	IM TE 300 mg/3wk	-3.51(-17.11,9.98)
IM TC 200 mg/2 wk		-15.06(-26.99,-3.12)
IM TC 200 mg/4 wk		-16.96(-28.18,-5.70)

IM TC 250 mg/2wk		-8.53(-19.81,2.78)
Durateston, IM, 250 mg/4wk		-16.59(-27.91,-5.27)
IM TC 200 mg/2 wk	IM TE 50-400 mg/1-2 wk	-11.55(-25.33,2.34)
IM TC 200 mg/4 wk		-13.45(-26.71,-0.08)
IM TC 250 mg/2wk		-5.01(-18.35,8.45)
Durateston, IM, 250 mg/4wk		-13.07(-26.35,0.29)
IM TC 200 mg/4 wk	IM TC 200 mg/2 wk	-1.90(-13.46,9.66)
IM TC 250 mg/2wk		6.53(-5.16,18.17)
Durateston, IM, 250 mg/4wk		-1.53(-13.18,10.07)
IM TC 250 mg/2wk	IM TC 200 mg/4 wk	8.44(-2.47,19.30)
Durateston, IM, 250 mg/4wk		0.37(-6.93,7.65)
Durateston, IM, 250 mg/4wk	IM TC 250 mg/2wk	-8.06(-19.21,2.97)

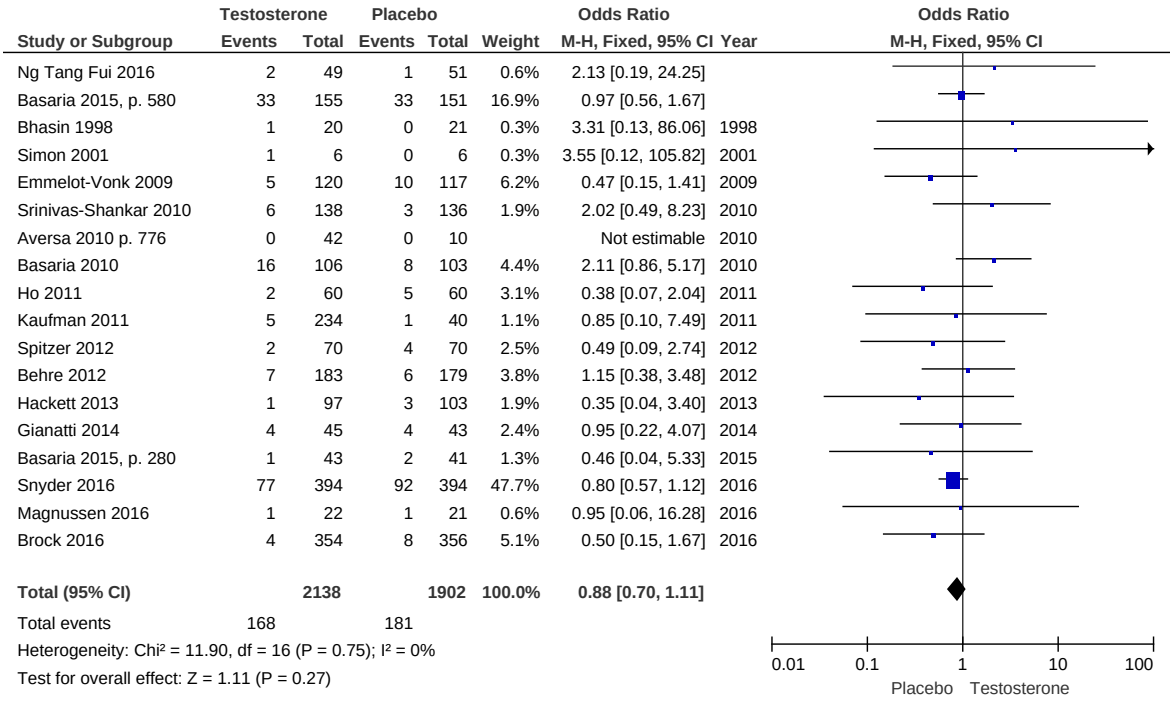
eFigure 6: Odds of myocardial infarction associated with the use of any testosterone v. placebo



eFigure 7: Odds of prostate cancer associated with the use of any testosterone v. placebo



eFigure 8: Odds of serious adverse events: any testosterone v. placebo

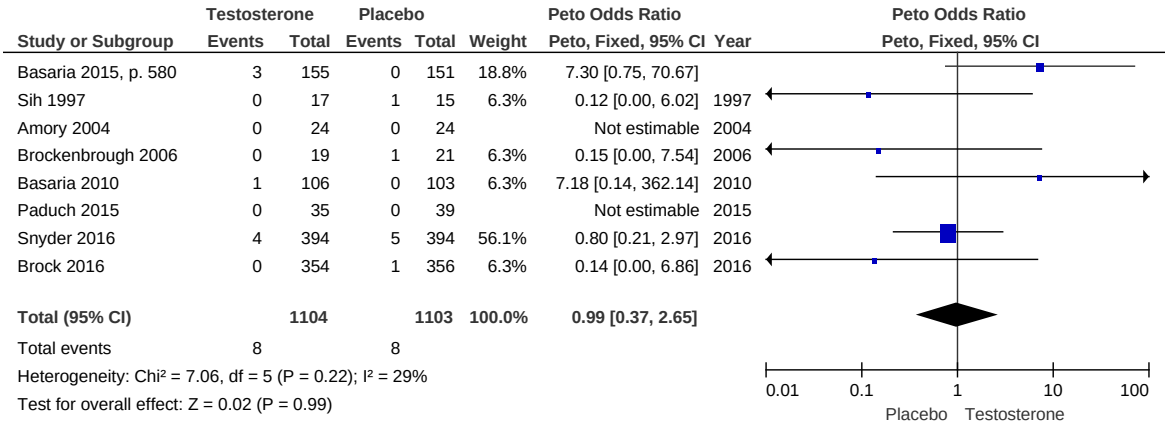


eTable 11: Odds of serious adverse events associated with individual testosterone products – Bayesian network meta-analysis

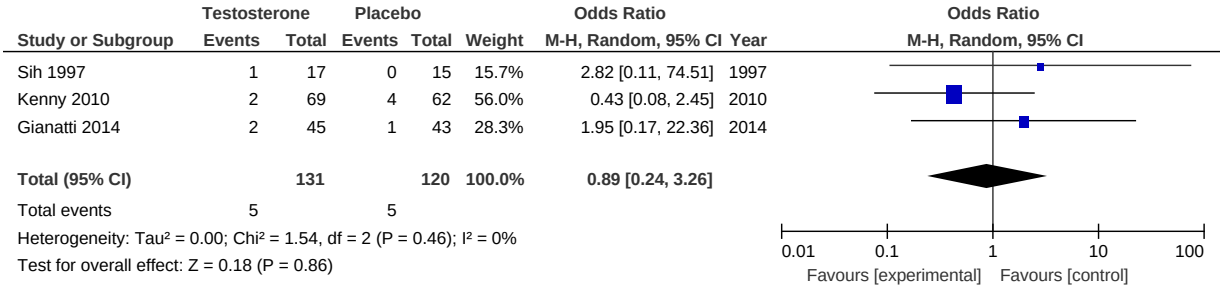
	Odds ratio (95% credible interval)*							
	Placebo	Gel 1%, 50 mg/d	Gel 1%, 75 mg/d	Gel 1%, 100 mg/d	Gel 1.62%, 40.5 mg/d	Solution 2%, 60 mg/d	Oral TU, 160 mg/d	IM TU, 1000 mg/12 wk
Gel 1%, 50 mg/d	0.91 (0.46,2.10)	—						
Gel 1%, 75 mg/d	0.98 (0.25,3.55)	1.08 (0.21,4.42)	—					
Gel 1%, 100 mg/d	1.41 (0.39,4.06)	1.54 (0.31,5.25)	1.45 (0.23,7.53)	—				
Gel 1.62%, 40.5 mg/d	1.19 (0.11,40.82)	1.30 (0.10,48.76)	1.24 (0.09,51.17)	0.89 (0.07,35.34)	—			
Solution 2%, 60mg/d	0.47 (0.08,2.53)	0.51 (0.07,3.07)	0.48 (0.06,4.08)	0.34 (0.04,2.88)	0.38 (0.01,7.32)	—		
Oral TU 160 mg/d	0.45 (0.08,2.17)	0.49 (0.07,2.67)	0.46 (0.05,3.60)	0.32 (0.05,2.51)	0.36 (0.01,6.21)	0.94 (0.09,10.03)	—	
IM TU,1000 mg/12 wk	0.68 (0.23,1.94)	0.74 (0.18,2.56)	0.69 (0.13,3.70)	0.48 (0.11,2.55)	0.56 (0.01,7.68)	1.43 (0.20,11.31)	1.50 (0.23,10.76)	—

Note: IM = intramuscular injection, TU = testosterone undecanoate.
*Random effects model. Significant changes are indicated by use of bold and colour (green indicates that the row treatment treatement is significantly better than the column treatment, while red indicates that the row treatment is significantly worse than the column treatment). White indicates no significant difference between treatments. An additional 4 RCTs (Aversa 2010; Schubert 2004; Bhasin 1998; Simon 2001) could not be included in the network because they reported zero events in ≥ treatment groups.

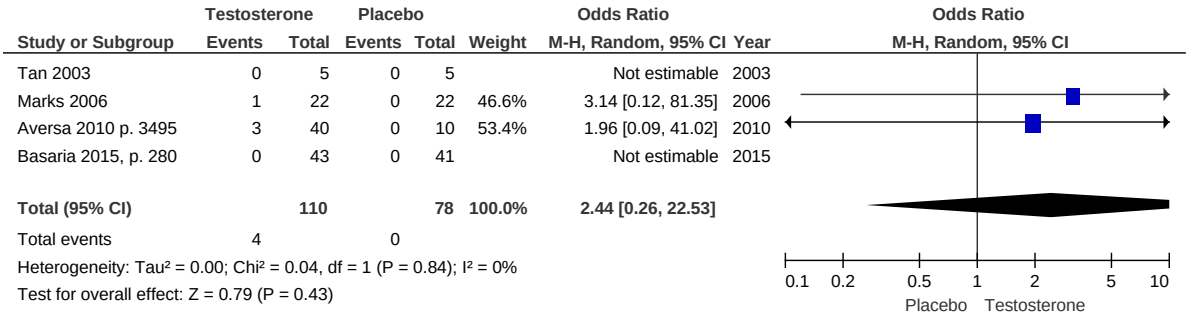
eFigure 9: Odds of stroke associated with the use of any testosterone v. placebo



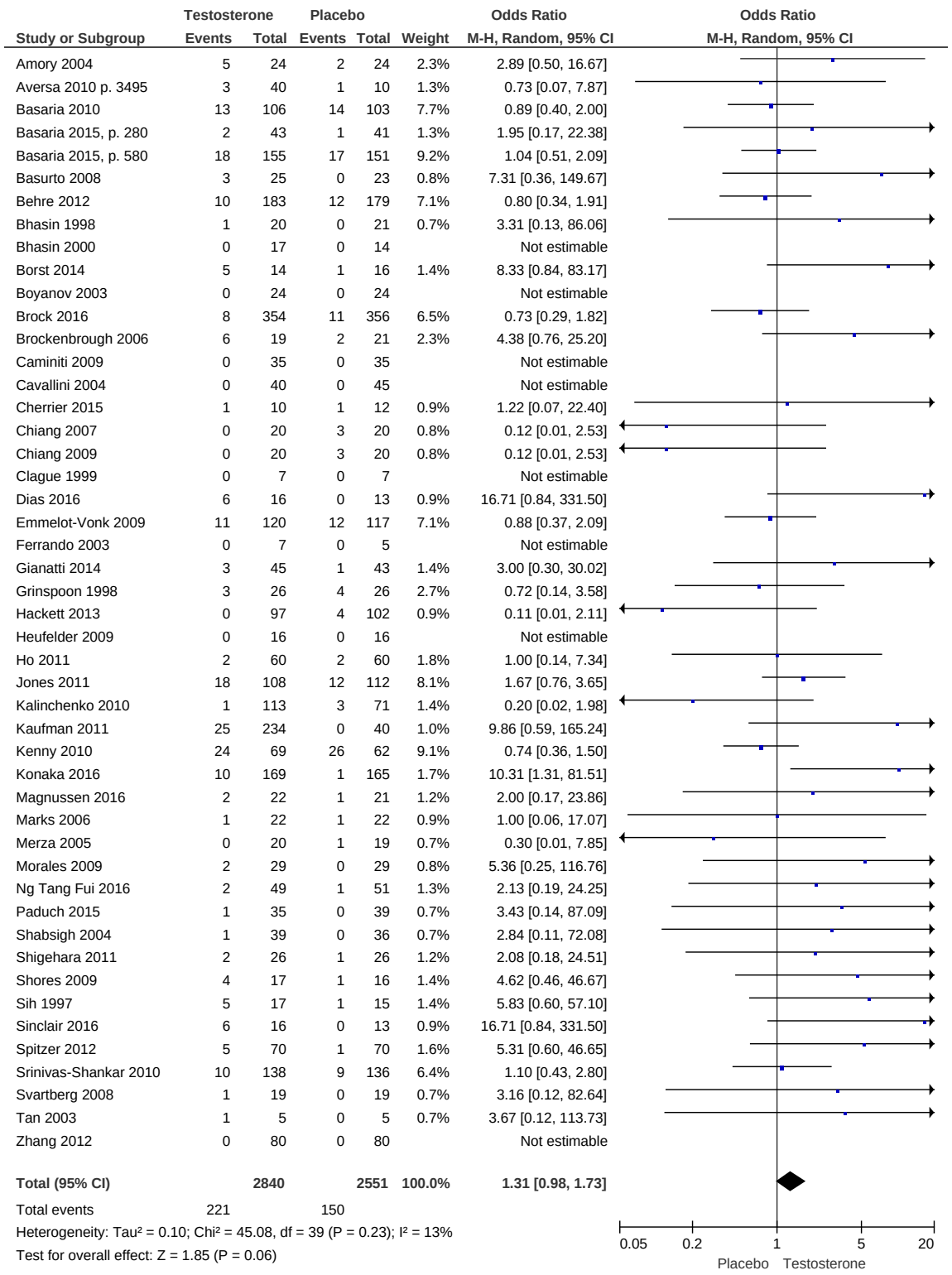
eFigure 10: Odds of heart disease associated with the use of any testosterone v. placebo



eFigure11: Odds of erythrocytosis associated with the use of any testosterone v. placebo



eFigure 12: Odds of withdrawals due to adverse events associated with the use of any testosterone v. placebo



eTable 12: Odds of withdrawals due to adverse events associated with individual testosterone products – Bayesian network meta-analysis

	Odds ratio (95% credible interval)*																
	Placebo	Patch, 5 mg/d	Gel 1%, 5 mg/d	Gel 1%, 50 mg/d	Gel 1%, 75 mg/d	Gel 1%, 100 mg/d	Gel 2%, 60 mg/d	Solution 2%, 60 mg/d	Oral TU 160 mg/d	IM TU, 1000 mg/10 wk	IM TU, 1000 mg/12 wk	IM TE, 125 mg/ wk	IM TE, 150 mg/ 2 wk	IM TE, 200 mg/ 2 wk	IM TE, 250 mg/ 4 wk	IM TE, 300 mg/ 3 wk	IM TC, 200 mg/ 2 wk
Patch, 5 mg/d	**6.82 (1.66, 32.14)**	—															
Gel 1%, 5 mg/d	0.76 (0.27, 2.14)	**0.11 (0.02, 0.63)**	—														
Gel 1%, 50 mg/d	1.45 (0.77, 3.00)	**0.21 (0.05, 0.86)**	1.91 (0.59, 6.89)	—													
Gel 1%, 75 mg/d	1.30 (0.55, 3.57)	0.19 (0.03, 1.07)	1.71 (0.46, 7.48)	0.90 (0.29, 2.85)	—												
Gel 1%, 100 mg/d	1.03 (0.45, 2.40)	**0.15 (0.03, 0.64)**	1.36 (0.37, 5.19)	0.71 (0.25, 1.90)	0.79 (0.22, 2.61)	—											
Solution 2%, 60 mg/d	1.64 (0.57, 4.95)	0.24 (0.04, 1.42)	2.18 (0.50, 9.67)	1.14 (0.30, 3.98)	1.26 (0.28, 4.94)	1.60 (0.40, 6.12)	—										
Gel 2%, 60 mg/d	0.73 (0.21, 2.37)	**0.11 (0.01, 0.67)**	0.96 (0.19, 4.68)	0.50 (0.12, 1.88)	0.56 (0.11, 2.35)	0.70 (0.16, 2.93)	0.44 (0.08, 2.23)	—									
Oral TU 160 mg/d	0.87 (0.28, 2.77)	**0.13 (0.02, 0.80)**	1.15 (0.25, 5.43)	0.60 (0.15, 2.23)	0.67 (0.14, 2.77)	0.84 (0.20, 3.54)	0.53 (0.11, 2.61)	1.20 (0.23, 6.61)	—								
IM TU, 1000 mg/10 wk	2.14 (0.18, 33.83)	0.31 (0.02, 7.21)	2.85 (0.20, 53.28)	1.48 (0.11, 24.89)	1.64 (0.12, 28.93)	2.08 (0.16, 37.59)	1.29 (0.09, 25.16)	2.95 (0.20, 59.09)	2.47 (0.17, 49.97)	—							
IM TU, 1000 mg/12 wk	0.52 (0.21, 1.26)	**0.08 (0.01, 0.40)**	0.69 (0.17, 2.72)	0.36 (0.11, 1.05)	0.40 (0.10, 1.36)	0.50 (0.15, 1.68)	0.31 (0.08, 1.28)	0.72 (0.16, 3.21)	0.59 (0.14, 2.52)	0.24 (0.01, 3.42)	—						
IM TE, 125 mg/ wk	7.95 (0.97, 105.20)	1.20 (0.09, 22.88)	**10.65 (1.03, 166.10)**	5.47 (0.60, 77.02)	6.08 (0.60, 90.45)	7.72 (0.80, 115.20)	4.89 (0.44, 78.95)	**11.35 (1.01, 179.70)**	9.32 (0.83, 152.60)	3.88 (0.11, 140.30)	**15.62 (1.59, 244.70)**	—					

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IM TE, 150 mg/ 2 wk	1.01 (0.04, 22.84)	0.15 (0.00, 4.20)	1.34 (0.05, 34.59)	0.70 (0.03, 16.50)	0.77 (0.03, 18.63)	0.97 (0.04, 24.53)	0.62 (0.02, 17.03)	1.39 (0.05, 39.21)	1.16 (0.05, 33.97)	0.46 (0.01, 25.13)	1.95 (0.08, 49.97)	0.12 (0.00, 4.99)	—				
IM TE, 200 mg/ 2 wk	2.83 (0.49, 21.73)	0.42 (0.04, 4.94)	3.78 (0.49, 36.13)	1.96 (0.29, 16.21)	2.17 (0.28, 19.79)	2.73 (0.39, 24.40)	1.73 (0.22, 17.02)	3.93 (0.48, 41.61)	3.26 (0.40, 32.63)	1.38 (0.05, 28.67)	5.50 (0.74, 50.37)	0.35 (0.02, 6.55)	2.92 (0.08, 107.60)	—			
IM TE, 250 mg/ 4 wk	5.92 (1.43, 36.28)	0.89 (0.10, 8.37)	**8.05 (1.33, 61.53)**	4.12 (0.82, 27.64)	4.61 (0.77, 32.91)	**5.81 (1.08, 41.07)**	3.66 (0.59, 29.86)	**8.31 (1.27, 72.32)**	**6.95 (1.08, 57.31)**	2.88 (0.11, 57.41)	11.75 (2.13, 84.99)	0.75 (0.04, 11.64)	6.10 (0.20, 202.50)	2.15 (0.18, 25.19)	—		
IM TE, 300 mg/ 3 wk	0.72 (0.11, 4.20)	**0.10 (0.01, 0.99)**	0.93 (0.11, 7.44)	0.49 (0.06, 3.19)	0.54 (0.07, 3.89)	0.69 (0.09, 4.94)	0.43 (0.05, 3.45)	0.98 (0.10, 8.51)	0.82 (0.09, 7.04)	0.33 (0.01, 6.96)	1.38 (0.18, 10.17)	0.09 (0.00, 1.40)	0.71 (0.02, 23.91)	0.24 (0.02, 2.99)	0.12 (0.01, 1.18)	—	
IM TC, 200 mg/ 2 wk	5.77 (0.72, 76.47)	0.85 (0.06, 15.32)	7.73 (0.72, 116.20)	3.98 (0.43, 54.25)	4.37 (0.43, 64.41)	5.53 (0.60, 78.93)	3.52 (0.33, 54.96)	8.03 (0.71, 131.40)	6.60 (0.62, 104.30)	2.73 (0.09, 84.03)	**11.06 (1.15, 170.30)**	0.72 (0.03, 19.57)	5.92 (0.14, 282.40)	2.07 (0.10, 43.57)	0.95 (0.06, 17.27)	8.60 (0.51, 180.50)	—

Note: IM = intramuscular injection, TC = testosterone cypionate, TE = testosterone enanthate, TU = testosterone undecanoate.

*Random-effects model. Significant changes are indicated by use of bold and colour (green indicates that the row treatment treatement is significantly better than the column treatment, which red indicates that the row treatment is signigicantly worse than the column treatment). White indicates no significant difference between treatments. An additional 23 studies (Basurto 2008, Bhasin 1998 (p. 140), Bhasin 1998 (p. 3155), Boyanov 2003, Caminiti 2009, Cavallini 2004, Chiang 2007, Chiang 2009, Clague 1999, Dobs 1999, Ferrando 2003, Hackett 2013, Heufelder 2009, Kaufman 2011, Merza 2005, Morales 2009, Schubert 2004, Shabsigh 2004, Svartberg 2008, Tan 2003, Zhang 2012, Dias 2016, Paduch 2015) were removed from the network meta-analysis because zero events were reported in one or both groups.

Supplemental Online Content: Elliott et al. Testosterone therapy in hypogonadal men: a systematic review and network meta-analysis.

eTable 13: Summary of harms outcomes reported in non-randomized studies

Author, year	Population	Treatment (no. in group)	Outcome	Comments
Retrospective cohort				
Cheetham 2017	≥ 40 yrs with documented androgen deficiency	• Ever TRT (8,808) • Never TRT (35,527) Mean follow-up: 4.4 years (median 3.4 years, IQR, 1.7-6.5 years)	• Stroke: AHR 0.64 (95% CI 0.52, 0.80) • Acute MI: AHR 0.74 (95% CI 0.63, 0.86) • CVD: AHR 0.76 (95% CI 0.61, 0.93)	Entry into cohort was based on filling a prescription for TRT (patch 13.6%, gel 34.7%, injectable 51.6%).
Layton 2015	New users of TRT*	• Gel (109,810) • Injection (103,555) • Patch (9,255) Mean treatment duration between 96 days (patch) and 122 days (injection)	Injection v. gel • MI: AHR 1.64 (95% CI 0.57 to 4.69) • Stroke: AHR 1.28 (0.27, 6.02)	No significant difference in MI or stroke between injection and gel users. No data available for patch v. injection or gel users.
Pastuszak 2015	New TRT users or had been off TRT for ≥ 3 or mo	• Gel (1% 50–100mg/d or 1.62% 20.25–80.1 mg/d) (47) • IM TE or TC, 100–200mg/wk (57) • Pellets (75mg/3–6 mo) (74) Duration: 36 mo	• Erythrocytosis: Gel: 12.8% of patients Injection: T 66.7% Pellets: 35.1% • Prostate cancer: 1 case of prostate cancer diagnosed in pellet group. No new cases of prostate cancer among men with previous prostate cancer.	Erythrocytosis defined as hematocrit ≥50%; Erythrocytosis occurred significantly earlier in the injection group (10.5±9.1 mo) compared with the gel (14.0±12.6 mo) or pellet (16.4 ±10.7mo) groups.
Ramasamy 2015	≥ 65 yr and ≥3 hypogonadal symptoms	• TRT, dose NR (153) • No TRT, dose NR (64) Duration: Median follow-up 3.8 (TRT) v. 3.4 yr (TRT)	•MI: 1 event in TRT group v. 0 in no TRT group • Stroke: 2 events in TRT v. 1 in no TRT group	All events (except 1 death which took place after 6 months of follow-up) occurred after 2 or more years.
Vigen 2013	Men who underwent coronary angiography	• TRT, dose NR (1223) • No treatment (7486) Mean follow-up: 840 d	• Cardiovascular events†: AHR 1.29, 95% CI 1.05 to 1.58	Entry into cohort was based on filling a prescription for TRT (patch, gel, injectable; brands NR). Data reported as TRT v. no TRT. Length of follow-up differed by group.
Shores 2012	> 40 yr treated at a VA medical center, inpatient or outpatient	• No treatment (633) • TRT (398) Duration: 20.2 mo	• Prostate cancer: No treatment: 13/633 men; TRT: 7/398 men	Data reported as TRT v. no TRT. TRTs included injectable, patch, or gel (brands NR)
Rhoden 2006	Negative prostate biopsy prior to starting TRT	• IM testosterone, dose and type NR (33) • Gel 1%, dose NR (25) Duration: 12 mo	• Prostate cancer: 1 case in the IM group	
Guay 2000	Men with ED and primary or secondary hypogonadism	• IM TE, 200–300 mg/2–3 wk (25) • Patch, 5 mg/d (16)	• Prostate cancer: 3 cases (NR which treatment group the patients belonged to)	

		Duration: 2–3 mo		
Prospective cohort				
Debruyne 2017	≥18 yr with a diagnosis of hypogonadism	• TRT, dose NR (750) • No TRT (249) Duration: 36 mo (23,900 person-mo)	• Prostate cancer: incidence rate ratio 0.52 (95% CI 0.22 to 1.26)	68% of TRT users recieved topical gels, 31% injectables, and 2% oral products
Traish 2017	Symptoms of hypogonadism	• TU, 1000mg/12wk (360) • No TRT (296) Median follow-up: 7 yr	• CVD: 0 in TU group v. 19 in no TRT group • Nonfatal MI: 0 in TU group v. 26 in no TRT group • Nonfatal stroke: 0 in TU group v. 30 in no TRT group • Prostate cancer: 7 in TU group v. 12 in no TRT group	CVD in no TRT group attributed to MI (5), stroke (4), heart failure (7), thromboembolism (2), lung embolism (1), and pneumonia and lung failure (1)
Yassin 2017	Treated or untreated hypogonadal men	• TRT, dose NR (42) • No treatment (162) Duration: 6 yr	• Prostate cancer: 7 (16.7%) in TRT group vs. 84 (51.9%) in untreated group	Data reported as a positive biopsy for prostate cancer; lower severity of prostate cancer in terms of staging and grading in the TRT group than in the untreated group
Jung 2016	Symptoms of hypogonadism	• TU, 1000 mg/3 mo + lifestyle modification (54) • Lifestyle modify (52) Treatment duration: 8 mo	• Prostate cancer: 0 in both groups • MI: 0 in both groups • Stroke: 0 in both groups	Prospective, placebo-controlled study
Francomano 2014	Severely obese men (mean BMI 42) with ≥ 2 symptoms of hypogonadism	• DPE (12) • DPE + IM TU, 1000 mg/12 wk (12) Duration: 54 wk + 24 wk observational period following withdrawal of treatment	• WAE: zero in both groups • SAE: zero in both groups	
Aydogdu 2013	IHH	• Sustanon, 250 mg/3wk (28) • Gel 1%, 50 mg/d (24) Duration: 24 wk	• SAE: zero in all groups	
Blick 2013	HIV/AIDS	• Androgel 1%, gel, 50 mg/d (92) • Testim 1%, gel, 50 mg/d (75) Duration: 12 mo	• Erythrocytosis: zero in both groups • Prostate cancer: zero in both groups • WAE: zero in both groups	
Aversa 2012	Middle-aged men with LOH and MetS	• No treatment (20) • IM TU, 12 wk (40) Duration: 36 mo	• MI: 1 in control group • Erythrocytosis: 4 in TU group	
Dean 2005	21–81 yr	• Gel 1%, 50 mg/d (NR) • Gel 1%, 100 mg/d (NR) Total: 371 men Duration: up to 12 mo	• Prostate cancer: 3 • WAE: 40 • SAE: 6	Reported only adverse events "judged related to study medication" and that affected >1% of study population.
Wang	19–68 yr	• Gel 1%, 50 mg/d (NR)	•Prostate cancer: 1 in 75 mg/d group,	

Supplemental Online Content: Elliott et al. Testosterone therapy in hypogonadal men: a systematic review and network meta-analysis.

2004		• Gel 1%, 75 mg/d (NR) • Gel 1%, 100 mg/d (NR) Total: 163 men Duration: 36 mo‡	2 in 100 mg/d group • Skin reactions: 12 men	
Hajjar 1997	Elderly men	• No treatment (27) • IM TE or TC 200mg/2-3 wk (45) Duration: at least 2 yr	• Myocardial infarction: 1 in TRT group • Stroke: No treatment: 1/23; TRT: 1/26 • Diabetes: No treatment: 0/23; TRT: 1/26 • Erythrocytosis¶: No treatment: 0/27; TRT: 11/45	Safety outcomes were reported based on a subset of people assigned to each group

Note: AHR = adjusted hazard ratio, DPE = diet plus exercise, ED = erectile dysfunction, IHH = idiopathic hypogonadotropic hypogonadism, IM = intramuscular injection, LOH = late-onset hypogonadism, MetS = metabolic syndrome, MI = myocardial infarction, NR = not reported, SAE = serious adverse event, TC = testosterone cypionate, TE = testosterone enanthate, TU = testosterone undecanoate, TRT = testosterone replacement therapy, T = testosterone, VA = Veterans Affairs, WAE = withdrawal due to adverse events.

*Data from MarketScan database. Data for these outcomes not reported for the Medicare or United Kingdom's CPRD databases.

†Composite outcome of all-cause mortality, myocardial infarction, and ischemic stroke. MI, stroke and CV death were also reported separately; however the length of observation time differed between groups.

‡ This study was completed after an initial 6-month randomized study for an additional 36 months; participants had a total of 42 months of gel exposure.

¶Reported as polycythemia for the treatment group. Zero count inferred for the control group.

PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	**p. 1**
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	**p. 3**
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known*, including mention of why a network meta-analysis has been conducted.*	**p. 6**
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	**p. 6**
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	**p. 2,5,6**
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*	**p. 6-7**
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify	**p. 7**

		additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Online supplement
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	**p. 7**
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	**p. 7**
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	**p. 8**
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	**p. 8-9**
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	**p. 7-8**
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	**p. 8-9**
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	**p. 8-9**
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	**p. 8-9**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	**p. 7-8**
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses;	**NA**

		• *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	
RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	**p. 10, Figure 1**
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	**Fig 3, supplement**
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	**Supplement (eAppendix 4)**
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	**Supplement (eTable 1,2)**
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	**Supplement (eTable 3,4)**
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	**Supplement**
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	**p. 9-13, supplement**
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	**p. 10, supplement (eAppendix 5)**
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	**p. 9, Supplement (eTable 3,4)**
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses*, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	**NA**

DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	**p. 13**
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	**p. 15**
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	**p. 15-16**
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	**p. 2**

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Testosterone therapy in hypogonadal men: a systematic review and network meta-analysis

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Complete List of Authors:	Elliott, Jesse; University of Ottawa Heart Institute; University of Ottawa, School of Epidemiology and Public Health, Kelly, Shannon; Ottawa Hospital Research Institute, Cardiovascular Research Methods Centre; University of Ottawa, School of Epidemiology and Public Health Millar, Adam; Mount Sinai Hospital, University of Toronto Peterson, Joan; Clinical Epidemiology Program, Ottawa Hospital Research Institute Chen, Li; University of Ottawa Heart Institute, Cardiovascular Research Methods Centre Johnston, Amy; Cardiovascular Research Methods Centre, University of Ottawa Heart Institute Kotb, Ahmed; University of Ottawa Heart Institute, Skidmore, Becky; Independent Information Specialist Bai, Zemin; University of Ottawa Heart Institute, Cardiovascular Research Methods Centre Mamdani, Muhammad; St Michael's Hospital, Li Ka Shing Knowledge Institute Wells, George ; University of Ottawa Heart Institute, Cardiovascular Research Methods Centre; University of Ottawa, School of Epidemiology and Public Health
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Testosterone therapy in hypogonadal men: a systematic review and network meta-analysis

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Jesse Elliott, Shannon E. Kelly, Adam C. Millar, Joan Peterson, Li Chen, Amy Johnston, Ahmed Kotb, Becky Skidmore, Zemin Bai, Muhammad Mamdani, George A Wells

Jesse Elliott MSc,
Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, 40 Ruskin Street, Ottawa, Ontario, K1Y4W7

Shannon Kelly MSc,
Cardiovascular Research Methods Centre, University of Ottawa Heart Institute,
40 Ruskin Street, Ottawa, Ontario, K1Y4W7

Adam C. Millar MD MScCH
Department of Medicine, Mount Sinai Hospital, University of Toronto, Toronto, Ontario

Joan Peterson BSc,
Clinical Epidemiology Program, Ottawa Hospital Research Institute, 1053 Carling Avenue, Ottawa, Ontario, K1Y 4E9

Li Chen MSc,
Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, 40 Ruskin Street, Ottawa, Ontario, K1Y4W7

Amy Johnston MSc,
Cardiovascular Research Methods Centre, University of Ottawa Heart Institute,
40 Ruskin Street, Ottawa, Ontario K1Y4W7

Ahmed Kotb MSc,
Royal College of Surgeons in Ireland, 123 St. Stephen's Green, Dublin, Ireland

Becky Skidmore MLS,
Independent Information Specialist, Ottawa, Ontario, K1T 3Z2

Zemin Bai MSc,
Cardiovascular Research Methods Centre, University of Ottawa Heart Institute,
40 Ruskin Street, Ottawa, Ontario K1Y4W7

Muhammad Mamdani PharmD,
Li Ka Shing Knowledge Institute, St. Michael's Hospital; Toronto, Ontario M5B1W8

George A. Wells PhD, Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, 40 Ruskin Street, Ottawa, Ontario, K1Y4W7

Correspondence to: GA Wells, gawells@ottawaheart.ca

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Ethical approval: not required.

Data sharing: No additional data available.

Registration: PROSPERO number: CRD42014009963

Competing interest statement: Dr. Mamdani reports receiving honoraria for serving on Advisory Boards for Astra Zeneca, Bristol-Myers Squibb, Eli Lilly and Company, GlaxoSmithKline, Hoffman La Roche, Novartis, Novo Nordisk, and Pfizer, outside the submitted work. Ms. Skidmore is a paid information consultant/contractor to the Ottawa Hospital Heart Institute. No conflicts declared by any other author.

Contributors: JE, SK, MM, and GW designed the study. BS developed and executed the search strategy. JE, SK, JP, AJ, AK, and ZB selected studies for inclusion and extracted data. JE, AK, and LC analyzed the data. JE, SK, LC, AM, and GW interpreted the data. JE wrote the first draft of the manuscript, which

was critically revised for intellectual content by all authors. All authors approved the final version submitted for publication and agree to be accountable for all aspects of the study.

Keywords: testosterone, benefits, depression, quality of life, erectile function, libido, harms, cardiovascular-related adverse events, systematic review, network meta-analysis

ABSTRACT

Objective: To assess the relative effects of individual testosterone products among hypogonadal men.

Design: Systematic review and network meta-analysis.

Methods: We searched MEDLINE, Embase, Cochrane CENTRAL, and grey literature (May 25, 2017) for randomized controlled trials (RCTs) and non-randomized studies (NRS) that involved hypogonadal men given testosterone replacement therapy (TRT) for ≥ 3 months. Comparators were placebo, another TRT, or the same product at a different dose. Outcomes were quality of life, depression, libido, erectile function, activities of daily living, and testosterone levels, as well as cardiovascular death, myocardial infarction, stroke, prostate cancer, heart disease, diabetes, serious adverse events, withdrawals due to adverse events, and erythrocytosis. RCT data were pooled via meta-analysis and network meta-analysis. Risk of bias was assessed using Cochrane's Risk of Bias tool (RCTs) and SIGN50 (NRS).

Results: 87 RCTs and 51 NRS were included. Most were at high or unclear risk of bias, with short treatment duration and follow-up. When compared as a class against placebo, TRT improved quality of life (standardized mean difference [SMD] -0.26, 95% confidence interval [CI] -0.41,-0.11), libido (SMD 0.33, 95%CI 0.16,0.50), depression (SMD -0.23, 95%CI -0.44,-0.01), and erectile function (SMD 0.25, 95%CI 0.10,0.41). Most individual TRTs were significantly better than placebo at improving libido (6/10). Only one TRT was better than placebo at improving quality of life, and no individual TRTs improved depression or erectile function. There was no increased risk of adverse events, with the exception of withdrawals due to adverse events with the use of some TRTs.

Conclusion: Despite a class effect of improving quality of life, depression, erectile function, and libido, major improvements were not observed with the use of any individual product. We observed no statistically significant increase in the risk of adverse events; however, longer-term high-quality trials are needed to fully assess the risk of harm.

Registration: PROSPERO CRD42014009963

Article Summary

Strengths and limitations

• We performed a comprehensive systematic review of the published and grey literature to identify randomized and non-randomized studies involving adult men with low testosterone levels.

• Although there is no universally agreed on level for the diagnosis of "low" testosterone, we included only studies that enrolled men with total testosterone ≤ 12 nmol/L or free testosterone ≤ 225 pmol/L, consistent with recent guidelines.

• Data from non-randomized studies were poorly reported and were not suitable to pooling via meta-analysis.

• The included studies were generally at high or unclear risk of bias, and most studies had a relatively short treatment and follow-up duration.

• Longer-term high-quality studies are needed to more fully assess the risk of rare adverse events.

Introduction

Testosterone deficiency has well-recognized negative effects on male sexuality and quality of life.[1] Recent clinical practice guidelines recommend testosterone replacement therapy (TRT) for adult men with low testosterone levels (hypogonadal men) with the goal of improving symptoms and elevating testosterone levels into the mid-normal range for young men.[2] However, two large observational studies have reported an increased risk of cardiovascular events with testosterone use,[3,4] and the US Food and Drug Administration (FDA) and Health Canada both have warned of a potential increased risk of cardiovascular events among men using testosterone products.[5,6]

Previous meta-analyses have reported positive effects of TRT compared with placebo on quality of life,[7] depression,[8,9] and some aspects of sexual function.[10] However, the results of individual trials have been mixed, and there is variation in testosterone formulations and doses.[11] Similarly, previous meta-analyses of potential harms related to TRT use have reported contradictory findings.[12–16] A 2013 meta-analysis reported an increased risk of cardiovascular-related events in a mixed population of hypogonadal and eugonadal men[15]; however, others have found no increased risk of cardiovascular outcomes, including myocardial infarction, stroke, or cardiovascular death.[12–14,16]

Because there are multiple TRT products and many different dosing strategies,[17] it may not be appropriate to group together all testosterone products, as in traditional meta-analyses. In this study, we performed a systematic review to identify randomized controlled trials (RCTs) and non-randomized studies (NRS) involving hypogonadal men, and we used network meta-analysis to compare each individual product.

Methods

This review was registered *a priori* (CRD42014009963) and followed the Cochrane handbook[18] and the PRISMA for Network Meta-Analysis checklist.[19] Our review included RCTs and NRS involving adult men with low testosterone taking any form of TRT compared to placebo, another TRT, or the same TRT at a different dose. We did not exclude studies on the basis of reported outcomes.

Patient involvement: No patients were involved in setting the research question or in developing plans for design, or implementation of the study. A patient representative was involved in selecting the outcome measures, and patient groups were given the opportunity to comment on the study protocol. No patients were asked to advise on the interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Search strategy: Using the OVID platform, we searched Ovid MEDLINE, Ovid MEDLINE In-Process & Other Non-Indexed Citations, and Embase Classic+Embase on June 3, 2014. We also searched CENTRAL in the Cochrane Library on Wiley on the same date. Grey literature were searched according to CADTH's Grey Matters Light.[20] All searches were updated on May 25, 2017.

We used controlled vocabulary, including "Testosterone", "Testosterone Congeners" and "Androgens", to which we applied relevant subheadings "administration & dosage", "analogs & derivatives", "adverse events" and "therapeutic use", or combined with "Hormone Replacement Therapy." Our keywords included "testosterone" or "androgen" in combination with means of administration (buccal, cream, gel, implant, injections, oral, patch, transdermal) or function (replacement, substitute, supplement, therapy, treatment). We also searched "TRT" and all known names for testosterone replacement products (e.g., androgel, Bio-T-Gel, Striant). Truncation, wildcards and proximity operators were incorporated as appropriate and terminology and syntax were adjusted according to database and platform. The search strategy is available in eAppendix1.

Study selection: We included placebo- and active-controlled RCTs and NRS involving adult men (≥ 18 yr) with low testosterone (total testosterone ≤ 12 nmol/L or free testosterone < 225 pmol/L) administered a testosterone product. We excluded studies that artificially suppressed endogenous testosterone, involved testosterone precursors, or had less than 10 participants. We included studies with a treatment duration of 12 weeks or longer, as follow-up is generally recommended for this time point.[2,21] Cross-over trials were included if the initial period was at least 12 weeks. Titles and abstracts were screened in duplicate (JE, JP,

ZB), and the full-text of any potentially relevant record was evaluated (JE, JP, AJ, ZB). Disagreements were resolved by consensus.

Data extraction and risk of bias: Data were extracted by one reviewer using piloted standardized abstraction forms (Distiller SR) and checked by a second reviewer (JE, JP, AJ, AK, ZB). First-period data were extracted from cross-over trials. Risk of bias was assessed by two reviewers using the Cochrane Collaboration's risk of bias tool for RCTs or SIGN50 for cohort studies.[22] Disagreements were resolved by discussion. Publication bias was assessed by visual inspection of funnel plots.

Outcomes: Outcomes of interest were quality of life, depression, libido, erectile function, activities of daily living, and total testosterone level (at 3 mo, 6 mo, end of study) (continuous outcomes), as well as cardiovascular death, myocardial infarction, stroke, prostate cancer, diabetes, heart disease, serious adverse events, withdrawals due to adverse events, and erythrocytosis (dichotomous outcomes). We included data for quality of life, depression, erectile function, and libido that had been measured using a validated scale (eAppendix2), and the direction of each scale was standardized before analysis. A higher effect estimate (e.g., positive SMD or MD) indicates improvement in libido, erectile function and testosterone level, and a lower effect estimate indicates improvement in quality of life and depression. Data from RCTs were included for quality of life, depression, libido, erectile function, and activities of daily living, and testosterone levels, and data from RCTs and NRS were included for harms outcomes.

Data analysis*:* The results of the included NRS are summarized narratively. Meta-analysis and network meta-analysis involving data from RCTs were performed as described below. We performed meta-analysis using RevMan (v.5.3; Cochrane Collaboration) and Bayesian network meta-analysis using WinBUGS (v.1.4.3; MRC Biostatistics Unit). Analyses were based on mean change from baseline for quality of life, depression, erectile function, libido, and on mean after-treatment values for total testosterone level. The number randomized was used as the denominator for quality of life, depression, libido, erectile function, and total testosterone level, and the number who received treatment was used for

harms. Two trials[23,24] were removed from the analyses because the data from these trials were outliers for each outcome and each had a considerable effect on heterogeneity. In an exploratory analysis, we removed trials enrolling men with major comorbidities (i.e., HIV/AIDS, osteoporosis, metabolic syndrome, type 2 diabetes, angina, Alzheimer's disease, heart failure, end-stage renal disease).

In the network meta-analysis, we used a binomial likelihood model for dichotomous outcomes and a normal likelihood model for continuous outcomes, allowing for the inclusion of multi-arm trials.[25] Network meta-analyses included all trials that reported each outcome with no restrictions based on comorbidities. Each dose of an individual testosterone product was included as a separate node in the evidence networks. A continuity correction was applied to adjust for zero events for harm outcomes. Assessment of model fit and choice of model (fixed v. random effects) was based on assessment of the deviance information criterion and comparison of residual deviance to the number of unconstrained data points.[25] Results are reported for the random-effects model. We derived point estimates and 95% credible intervals (CrIs) using the Markov Chain Monte Carlo method. Mean differences (MDs), standardized mean differences (SMDs) with standard deviations (SDs) or odds ratios (ORs) with 95% CrIs or CIs are reported for continuous or dichotomous outcomes as appropriate. Vague priors (e.g., $N[0, 100^2]$) were assigned for basic parameters throughout.[25] To ensure model convergence, trace plots and Brooks-Gelman-Rubin statistics were assessed.[26] Three chains were fit for each analysis with at least 20,000 iterations and a burn-in of at least 20,000 iterations. Inconsistency was assessed where possible by comparing the deviance, between-study variance, and deviance information criterion statistics of the consistency and inconsistency models.[27] The posterior mean deviance of the individual data points in the inconsistency model was plotted against the posterior mean deviance in the consistency model.[27] All network diagrams were constructed using NodeXL.

Role of the funding source: The funder had no role in study design, data collection, analysis, interpretation, or writing. All authors had full access to the study data, and the corresponding author had final responsibility for the decision to submit for publication.

Results

Search results and study characteristics

We identified 87 RCTs and 51 NRS published between 1997 and 2017, corresponding to 196 records (Figure 1, eAppendix 3). Of these, 70 RCTs and 19 NRS reported an outcome of interest (eTable1,2). The median treatment duration of the RCTs was 6 months (range: 3–36 mo), with mean participant age ranging between 30 and 78 years (eAppendix 4, eTable1). Most RCTs were placebo controlled (87%), with 2 treatment groups (89%). Of the included NRS, 10 were retrospective and 9 were prospective cohorts, with a duration up to 8 years (eTable2). Few RCTs or NRS were at low risk of bias, primarily because of a lack of details about randomization procedures, allocation concealment, and analysis populations (eTable3,4). Based on visual inspection of funnel plots, publication bias could not be ruled out for most outcomes (eAppendix 5).

Network consistency

Comparison of the consistency and inconsistency models for libido and total testosterone levels did not show evidence of inconsistency (eAppendix6). Consistency could not be evaluated for quality of life, depression, or erectile function because of a lack of closed loops. The full network characteristics and evidence networks are presented in eAppendix7 and eFigure 1A-1E.

Outcomes

Quality of life: In total, 23 RCTs (21 placebo-controlled, 2 active-controlled) involving 3090 participants assessed quality of life. Compared with placebo, treatment with any TRT significantly improved quality of life (SMD –0.26, 95%CI –0.41,–0.11; n = 2834) with substantial heterogeneity (I^2 = 71%; Figure 2).

To explore this heterogeneity, we excluded RCTs that involved men with major comorbidities. This had little effect on heterogeneity (I^2 = 62%) or the point estimate (SMD –0.17, 95%CI –0.34,–0.01; eFigure 2).

The evidence network for quality of life comprised 23 RCTs, representing 14 treatments in addition to placebo (Figure 3). Intramuscular (IM) testosterone undecanoate (TU; 1000 mg/12 wk) significantly improved quality of life relative to placebo (SMD -0.48, 95%CI -0.84, -0.10) and to oral TU (160 mg/d; SMD -0.68, 95%CI -1.32, -0.02), with no other significant differences among the other treatments (Table 1). The results were consistent when studies involving men with major comorbidities were removed from the network, despite 3 fewer treatments being included in the network (data not shown).

Depression: Twelve RCTs (11 placebo-controlled, 1 active-controlled) involving 852 participants randomized to 9 treatments evaluated depression. Compared with placebo, treatment with any TRT improved depression (SMD –0.23, 95%CI –0.44,-0.01; n = 786;I^2 = 44%) (eAppendix 8 [eFigure3A]). Removal of trials involving men with major comorbidities did not reduce heterogeneity although the effect of TRT was no longer statistically significant (SMD –0.12, 95%CI –0.49,0.26; I^2 = 56%) (eFigure3B).

In the network meta-analysis, there were no significant differences in depression for any individual TRT compared with placebo or among the treatments (eTable5). Removal of trials involving major comorbidities did not alter the results (2 treatments removed; data not shown).

Libido: Fourteen RCTs (12 placebo-controlled, 2 active-controlled) involving 3167 patients randomized to 10 treatments investigated libido. Compared with placebo, treatment with any TRT significantly improved libido (SMD 0.33, 95%CI 0.16,0.50; I^2 = 74%; n = 2732) (eFigure4A). Removal of trials involving men with major comorbidities increased heterogeneity (I^2 = 80%), and the point estimate was no longer statistically significant (SMD 0.19, 95%CI –0.03,0.41) (eFigure4B).

In the network meta-analysis, most individual treatments significantly improved libido compared with placebo (6/10 treatments; eTable6). Among the treatments, 1% gel (100 mg/d) was significantly better than patch (5 mg/d) and oral TU (160 mg/d), and oral TU (120 mg/d) was significantly better than patch (5 mg/d) and 1% gel (75 mg/d). Oral TU (160 mg/d) was significantly worse than most other TRTs in the network (8/9 TRTs) (eTable6). Removal of trials involving major comorbidities resulted in the removal of 4 treatments from the network; however, the results were consistent for the remaining treatments (data not shown).

Erectile function: 17 RCTs (all placebo-controlled) involving 3165 patients randomized to 9 treatments evaluated erectile function. Compared with placebo, treatment with any TRT improved erectile function (SMD 0.25, 95%CI 0.10, 0.41), with substantial heterogeneity (I^2 = 74%; eFigure5A). Removing trials involving men with major comorbidities reduced heterogeneity (I^2 = 58%), with no qualitative change to the point estimate (SMD 0.36, 95%CI 0.21, 0.51; eFigure5B).

In the network meta-analysis, there were no significant differences in erectile function between placebo and any individual TRT or among the treatments (eTable7). Removal of trials involving major comorbidities did not alter the results (2 treatments removed; data not shown).

Activities of daily living: One RCT reported no significant difference in activities of daily living among men with mild cognitive impairment following 6 months of TRT (testosterone gel 50–100 mg/d) compared with placebo (p = 0.31).[28]

Testosterone levels: In total, 26 and 23 RCTs reported total testosterone levels after 3 or 6 months of treatment, respectively. End of treatment testosterone levels were reported in 57 RCTs. After 3 or 6 months of treatment, about half of the treatments in each network were associated with significantly higher total testosterone levels compared with placebo (3 mo: 6/15; 6 mo: 11/18) (eTables 8,9). By the end of treatment (12 wk to 36 mo), most products were associated with total testosterone above 12

nmol/L (26/28 testosterone therapies), and 17 of 28 treatments had significantly higher levels relative to placebo (eTable10).

Cardiovascular death: 10 RCTs reported the occurrence of cardiovascular death during the treatment period, while an additional 9 trials reported that no CV deaths had occurred (18 placebo-controlled RCTs). Compared with placebo via pair wise meta-analysis, there was no significant difference in the risk of cardiovascular death between placebo and any TRT (all products grouped together) (OR 2.15, 95% CI 0.72,6.45; I^2 = 11%) (Figure 4; Table 2). Because of the low event rate, network meta-analysis did not provide robust estimates for this outcome (data not reported).

Other adverse events: Compared with placebo via meta-analysis, there were no increased odds of myocardial infarction, stroke, prostate cancer, heart disease, erythrocytosis, or serious adverse events, with the use of any TRT product (Table 2; eFigure 6-11). Although not statistically significant, withdrawals due to adverse events tended to be significantly higher among TRT users compared with placebo (OR 1.31, 95% CI 0.98, 1.73; I^2 = 13%)(eFigure12). No RCTs reported incident diabetes during the treatment period.

Owing to the low event rates for most outcomes, network meta-analysis was only possible for serious adverse events and withdrawals due to adverse events. In the head-to-head comparison of TRTs, there was no significant difference in serious adverse events between any TRT and placebo or among the TRTs (eTable11). Use of testosterone patch (5 mg/d) was associated with an increased odds of withdrawal due to adverse events compared with placebo and many of the other TRTs (eTable12).

Nonrandomized studies

The reporting of harms in the included NRS was generally poor, primarily because of a lack of transparency around the number of patients assigned to each group, the number of events per group, and/or the type or dose of TRT (eTable13). In the longest prospective cohort study, involving 656 men

followed for up to 10 years,[29] men who had received IM TU (1000 mg/12 wk) were at lower risk of death (incidence of death: TRT group 0.0092 [95%CI 0.0032,0.0368]; no TRT group 0.1145 [95%CI 0.0746, 0.1756]), with 19 of 21 deaths in the control group attributed to cardiovascular causes and zero of 2 deaths in the TRT group due to cardiovascular causes. Non-fatal MI and non-fatal stroke were also more common in the untreated group than in the TRT group (TRT group: 0 MI, 0 stroke; no TRT group: 26 MI, 30 stroke). In a large retrospective cohort study in the US involving 8808 men dispensed a TRT product and 35,527 men never dispensed TRT,[30] men in the TRT group were at lower risk of sudden cardiovascular death (adjusted hazard ratio [aHR] 0.76, 95%CI 0.61, 0.93), acute MI (aHR 0.74; 95%CI 0.63, 0.86), and stroke (aHR 0.64, 95% CI 0.52, 0.80) over a median follow-up time of 3.4 years. In contrast, an earlier retrospective cohort study involving among 8709 men who had undergone angiography reported that those who had filled a prescription for TRT were at higher risk of an adverse cardiovascular event (aHR 1.29, 95%CI 1.05,1.58) compared men with no TRT prescription.[3] Concerning the relative safety of the different TRTs, one retrospective cohort study[31] reported no significant difference in risk between injection or gel TRT users with low testosterone at baseline for MI (aHR1.64, 95%CI 0.57, 4.69) stroke (aHR 1.28, 0.27, 6.02), or death (a HR 5.53, 95% CI 0.98, 31.15).

Prostate cancer was reported by 10 NRS.[29,32–40,41] In a large prospective registry involving 999 newly diagnosed hypogonadal men,[37] there was no statistically significant difference in the risk of prostate cancer between men who used or did not use TRT (incidence rate ratio 0.52, 95%CI 0.22, 1.26). Traish and colleagues[29] also reported fewer cases of prostate cancer among men who received TRT (IM TU) compared with hypogonadal men who did not receive TRT (TU: 7/360 men v. no TRT: 12/296 men) over a median follow-up of 7 years, and Yassin and colleagues[35] reported positive biopsies for prostate cancer among 16.7% of TRT users compared with 51.9% of non-users, as well as a lower severity in terms of staging and grading in their prospective study of prostate cancer among hypogonadal men. Among men with a previous diagnosis of prostate cancer, one small retrospective cohort study[41] reported no recurrences of prostate cancer among TRT users during the follow-up period (36 months). The reporting

of outcomes and treatment group in most of the remaining studies was poor: either the group assignment of the men who experienced prostate cancer or the number of men in each treatment group was not reported in each (eTable13).[33,34,38]

DISCUSSION

Despite more than 70 years of clinical use, TRT remains a controversial topic. Part of the controversy may be a result of different actions of the various testosterone preparations. In an attempt to clarify the benefits and harms of individual testosterone products, we used traditional pair-wise meta-analysis as well as network meta-analysis, which allows the relative comparison of products that have not been compared in head-to-head trials. Consistent with most previous meta-analyses,[8,7,10] we found that the use of TRT improved quality of life, depression, libido, and erectile function, with no increase in cardiovascular death or other major adverse events.

In the head-to-head comparison of individual testosterone treatments, we found no significant differences among products in their effect on depression or erectile function. For libido, testosterone gel (1%, 100 mg/d) was significantly better than testosterone patch (5 mg/d) and oral TU (160 mg/d). Oral TU (160 mg/d) was significantly worse than most other treatments in the network, including oral testosterone undecanoate at 120 mg/d. The finding that a lower dose of oral TU was more effective than a higher dose was unexpected and requires further investigation.

Conflicting data exist about the risk of adverse cardiovascular events among TRT users. The FDA and Health Canada both issued alerts in 2015 based in part on the findings of two observational studies.[3,4] In their retrospective cohort, Vigen and colleagues[3] included men with low testosterone who had undergone angiography, reporting an increased risk of a composite cardiovascular outcome that included all-cause mortality, myocardial infarction, and stroke (aHR 1.29, 95%CI 1.04, 1.58). Most participants in this study were receiving TRT in the form of a patch (63%) and had significant medical comorbidities, which may limit generalizability. The retrospective study by Finkle and colleagues[4] did not report the baseline

testosterone level of men in their cohort nor was the cohort restricted to men with androgen deficiency; as such, this study was not eligible for inclusion in our review, but their findings that the risk of non-fatal MI is increased in the first 90 days following testosterone prescription is concerning. However, other recent large observational studies have reported a lower risk of cardiovascular death, stroke and MI among TRT users,[29,30] supporting the findings of earlier observational studies that reported a lower risk of all-cause death among hypogonadal men using TRT. [40]

Previous meta-analyses have also reported contradictory findings concerning the risk of adverse events among TRT users. One meta-analysis reported an increase risk of cardiovascular adverse events among men using TRT,[15] while a number of other meta-analyses have found no increased risk of cardiovascular events among TRT users.[12–14,16,42,43] The meta-analysis by Xu and colleagues[15] involved a broad composite outcome (cardiac disorder, cardiovascular complaints, cardiovascular events, vascular disorders) and has been criticized for use of a fixed-effects model: subsequent reanalysis using a random-effects model found no significant increase in the risk of cardiovascular events.[43] Our findings are consistent with previous meta-analyses that have found no increased risk of individual cardiovascular events compared with placebo.[12–14,16,42,43]

Although we had intended to analyze the effects of individual testosterone products among men aged 65 years and older, data were limited because most RCTs included a wide age range. The Testosterone Trials were designed to address this lack of data among elderly men.[44] After one year of treatment with 1% testosterone gel, improved desire and erectile function were reported among men with low sexual function at baseline, with no apparent increase in the risk of adverse cardiovascular events.[44] Although these findings are encouraging, the trials were not powered to detect adverse events, and the results should not be generalized to different testosterone preparations.

Strengths and limitations

The strengths of this study include a comprehensive search of the published and grey literature without language or date restrictions. In contrast with some previous reviews, we included only studies that enrolled men with total testosterone ≤ 12 nmol/L or free testosterone ≤ 225 pmol/L. Although there is no universally agreed on threshold value for low testosterone, a recent guideline recommends TRT for men with total testosterone lower than 12 nmol/L.[11]

Our study had several limitations. First, the included studies used a variety of assays to determine testosterone levels and a variety of cut-off values for determining "low" testosterone. This has been noted by others.[11,45] The US Centers for Disease Control and Prevention's Hormone Standardization Project[46] will help to resolve this issue. Second, the included RCTs and NRS were generally at unclear or high risk of bias, which may have an impact on the reliability of subjective data. Third, the duration of treatment and the length of follow-up may have been too short to see an effect of TRT for all outcomes, including adverse events. In keeping with the recommendation to reassess symptoms after 3 months of TRT,[21] we included only studies with a treatment duration of 3 months or longer. The median duration of treatment was 6 months in the RCTs, but it is possible that some symptoms may take longer to resolve. Fourth, although some individual RCTs showed a positive effect of TRT on depression and erectile function compared with placebo, in the network meta-analysis no individual TRTs showed a positive effect compared with placebo. This phenomenon has been noted in previously and results in a more conservative estimate of effect.[47]

Conclusions

To the best of our knowledge, this is the first study to compare the benefits and harms of individual testosterone products among hypogonadal men. Our study builds on previous meta-analyses by comparing the relative effects of individual testosterone treatments, most of which have never been compared in head-to-head trials. When considered as a class (any TRT compared to placebo), TRT improved quality of life, depression, erectile function, and libido; however, when the individual products

were compared head to head, there were few differences between the treatments. We found no increased risk of major harms; however, this must be viewed in light of the high risk of bias of the included studies, the rare nature of serious harms, and the short treatment duration and follow-up of most studies. Future studies need to be rigorous in design and delivery, and include comprehensive descriptions of all aspects of methodology to further enable appraisal and interpretation of results.

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Figure legends

Figure 1: PRISMA flow diagram showing selection of studies.

Figure 2: Meta-analysis of the effect of testosterone on quality of life.

Figure 3: Evidence network for quality of life. The size of each circle (node) is proportional to the number of randomly assigned patients and indicates sample size. The number of randomized controlled trials that contributed to each direct comparison is indicated on the line between nodes. IM = intramuscular injection, TC = testosterone cypionate, TE = testosterone enanthate, TU = testosterone undecanoate.

Figure 4: Odds of cardiovascular death associated with the use of any testosterone product v. placebo

Tables

Table 1: Quality of life – Indirect comparison of testosterone products

Standardized mean difference (95% confidence interval)*

	Placebo	Patch, 5 mg/d	Gel 1%, 5 mg/d	Gel 1%, 50 mg/d	Gel 1%, 75 mg/d	Gel 1%, 100 mg/d	Gel 2%, 60 mg/d	Oral TU, 160 mg/d	IM TU, 1000 mg/ 10 wk	IM TU, 1000 mg/ 12 wk	IM TE, 250 mg/ 3 wk	IM TE, 250 mg/ 4 wk	IM TC, 200 mg/ 4 wk	IM Sustanon, 100 mg/2 wk	IM Durateston, 250 mg/4 wk
Patch, 5 mg/d	-0.33 (-0.97, 0.31)	—													
Gel 1%, 5 mg/d	-0.11 (-0.86, 0.64)	0.21 (-0.78,1.20)	—												
Gel 1%, 50 mg/d	-0.32 (-0.74, 0.17)	0.01 (-0.76,0.82)	-0.20 (-1.05,0.69)	—											
Gel 1%, 75 mg/d	-0.24 (-0.83, 0.34)	0.09 (-0.78,0.95)	-0.12 (-1.09,0.82)	0.08 (-0.70,0.79)	—										
Gel 1%, 100 mg/d	-0.19 (-0.94, 0.55)	0.13 (-0.84,1.10)	-0.08 (-1.13,0.97)	0.12 (-0.78,0.96)	0.04 (-0.89,0.99)	—									
Gel 2%, 60 mg/d	-0.29 (-1.01,0.44)	0.04 (-0.93,1.00)	-0.17 (-1.21,0.87)	0.03 (-0.85,0.86)	-0.05 (-0.96,0.89)	-0.09 (-1.12,0.94)	—								
Oral TU, 160 mg/d	0.20 (-0.33,0.74)	0.53 (-0.30,1.36)	0.32 (-0.61,1.24)	0.52 (-0.21,1.19)	0.44 (-0.34,1.24)	0.40 (-0.51,1.31)	0.49 (-0.41,1.38)	—							
IM TU, 1000 mg/10 wk	-0.21 (-0.96, 0.56)	0.12 (-0.87,1.13)	-0.09 (-1.15,0.98)	0.11 (-0.80,0.98)	0.03 (-0.92,1.00)	-0.01 (-1.07,1.06)	0.08 (-0.97,1.14)	-0.41 (-1.35,0.53)	—						
IM TU, 1000 mg/12 wk	**-0.48 (-0.84,-0.10)**	-0.15 (-0.89,0.60)	-0.36 (-1.19,0.48)	-0.16 (-0.76,0.41)	-0.24 (-0.91,0.47)	-0.28 (-1.10,0.55)	-0.19 (-1.00,0.62)	**-0.68 (-1.32,-0.02)**	-0.27 (-1.12,0.58)	—					
IM TE, 250 mg/3 wk	-0.05 (-1.04,0.94)	0.28 (-0.47,1.03)	0.07 (-1.17,1.30)	0.27 (-0.85,1.33)	0.19 (-0.95,1.34)	0.15 (-1.09,1.37)	0.24 (-1.00,1.46)	-0.25 (-1.38,0.88)	0.16 (-1.10,1.40)	0.43 (-0.63,1.49)	—				
IM TE, 250 mg/4 wk	0.08 (-0.44,0.63)	0.41 (-0.41,1.26)	0.20 (-0.72,1.13)	0.40 (-0.32,1.09)	0.32 (-0.44,1.13)	0.28 (-0.62,1.21)	0.37 (-0.51,1.28)	-0.12 (-0.86,0.66)	0.29 (-0.64,1.22)	0.56 (-0.09,1.22)	0.13 (-0.97,1.27)	—			
IM TC, 200 mg/4 wk	0.12 (-1.00,1.25)	0.45 (-0.83,1.74)	0.24 (-1.10,1.59)	0.44 (-0.78,1.64)	0.36 (-0.89,1.63)	0.32 (-1.03,1.66)	0.41 (-0.92,1.74)	-0.08 (-1.32,1.18)	0.33 (-1.01,1.68)	0.60 (-0.46,1.67)	0.17 (-1.32,1.66)	0.04 (-1.20,1.28)	—		
IM Sustanon, 100 mg/2 wk	-0.28 (-1.17,0.62)	0.05 (-1.05,1.14)	-0.16 (-1.32,1.01)	0.04 (-0.99,1.02)	-0.04 (-1.10,1.03)	-0.08 (-1.24,1.09)	0.01 (-1.13,1.16)	-0.48 (-1.52,0.57)	-0.07 (-1.24,1.11)	0.20 (-0.77,1.16)	-0.23 (-1.56,1.11)	-0.36 (-1.42,0.67)	-0.40 (-1.84,1.02)	—	
IM Durateston 250 mg/4wk	-0.37 (-1.49,0.74)	-0.05 (-1.33,1.24)	-0.26 (-1.61,1.09)	-0.06 (-1.27,1.12)	-0.14 (-1.37,1.13)	-0.18 (-1.51,1.16)	-0.08 (-1.40,1.23)	-0.57 (-1.81,0.66)	-0.17 (-1.52,1.17)	0.10 (-0.95,1.15)	-0.33 (-1.81,1.17)	-0.46 (-1.70,0.76)	-0.50 (-1.52,0.52)	-0.10 (-1.52,1.33)	—

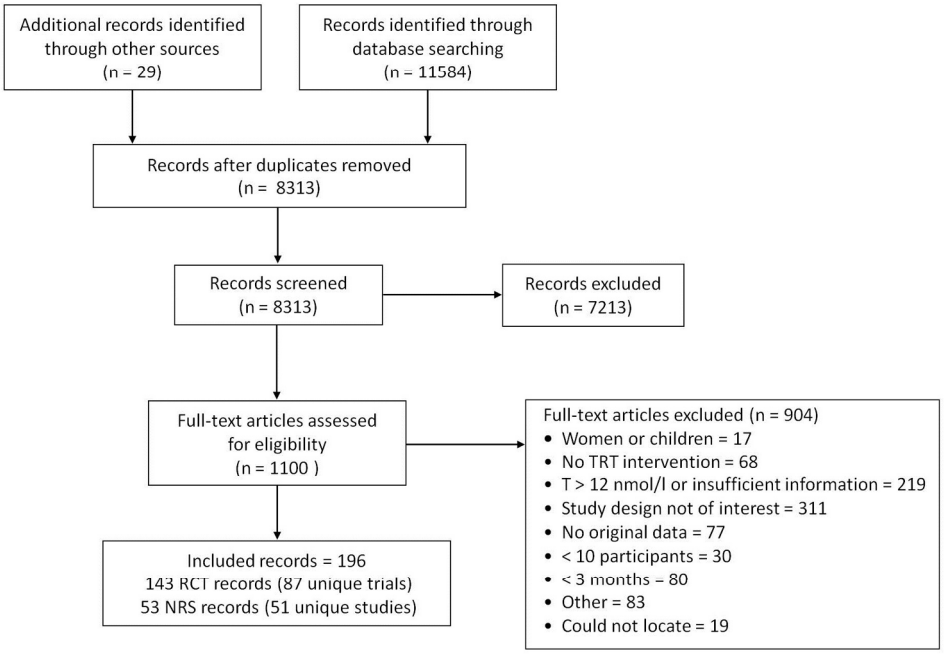
Note: IM = intramuscular injection, TC = testosterone cypionate, TE = testosterone enanthate, TU = testosterone undecanoate.

*Random-effects model, with analysis based on mean change from baseline. A negative standardized mean difference indicates improvement in quality of life. Statistically significant changes are indicated by use of bold and colour (green indicates that the row treatment is significantly better than the column treatment), and white indicates no statistically significant difference between treatments.

Table 2: Meta-analysis of adverse events associated with the use of any testosterone compared with placebo

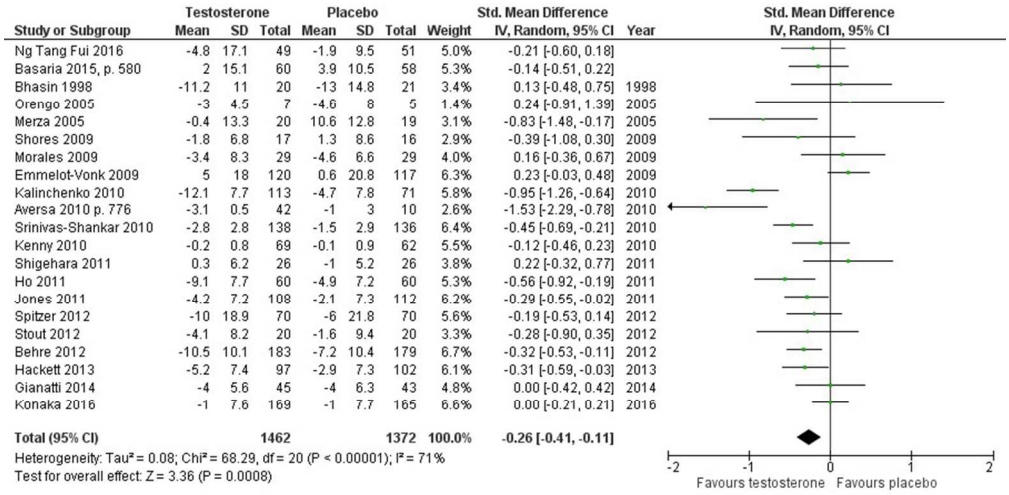
Outcome	No. of RCTs	Treatment duration	Event/no. treated	Odds ratio (95% CI)*	I^2
Cardiovascular death	18	12 wk to 36 mo	Placebo: 4/1851 TRT: 9/2088	2.15 (0.72, 6.45)	11%
Myocardial infarction	15	12 wk to 36 mo	Placebo: 10/1613 TRT: 6/1915	0.43 (0.15, 1.19)	34%
Prostate cancer	13	12 wk to 36 mo	Placebo: 11/1649 TRT: 12/1877	0.97 (0.43, 2.23)	0%
Stroke	8	12 wk to 36 mo	Placebo: 8/1103 TRT: 8/1104	0.99 (0.37, 2.65)	29%
Heart disease	3	40 wk to 12 mo	Placebo: 5/120 TRT: 5/131	0.89 (0.24 to 3.26)	0%
Erythrocytosis	4	12 wk to 12 mo	Placebo: 0/78 TRT: 4/110	2.44 (0.26, 22.53)	0%
Diabetes	0	—	—	—	—
Serious adverse events	18	12 wk to 36 mo	Placebo: 181/1902 TRT: 168/2138	0.88 (0.70, 1.11)	0%
Withdrawals due to adverse events	48	12 wk to 36 mo	Placebo: 150/2551 TRT: 221/2840	1.31 (0.98, 1.73)	13%

Note: CI = confidence interval, RCT = randomized controlled trial, TRT = testosterone replacement therapy.
*Random-effects models.



PRISMA flow diagram showing selection of studies.

165x117mm (300 x 300 DPI)



Meta-analysis of the effect of testosterone on quality of life.

76x37mm (300 x 300 DPI)

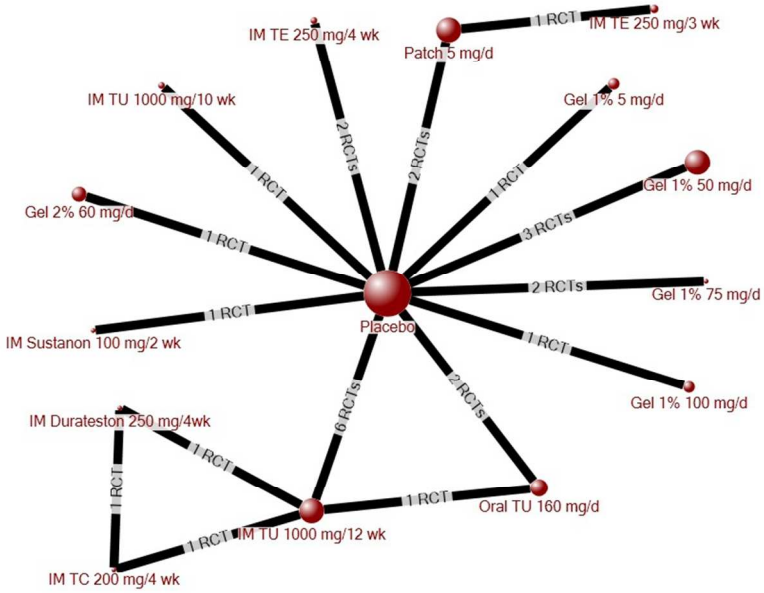
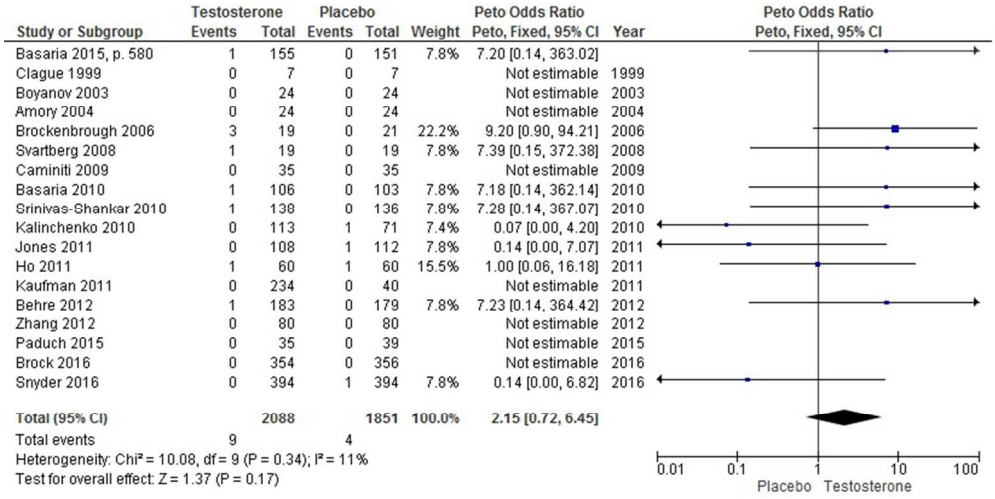


Figure 3: Evidence network for quality of life. The size of each circle (node) is proportional to the number of randomly assigned patients and indicates sample size. The number of randomized controlled trials that contributed to each direct comparison is indicated on each line. IM = intramuscular injection, TC = testosterone cypionate, TE = testosterone enanthate, TU = testosterone undecanoate.

89x57mm (300 x 300 DPI)



Odds of cardiovascular death associated with the use of any testosterone product v. placebo

70x35mm (300 x 300 DPI)

Supplementary Online Content:

Elliott et al. Testosterone replacement therapies in hypogonadal men: a systematic review and network meta-analysis

eAppendix 1: Search strategy

The search was originally executed on June 3, 2014 and updated May 25, 2017.

Testosterone Replacement Therapy
Primary Studies - Final Strategies
2014 Jun 3

Database: Embase Classic+Embase <1947 to 2014 June 02>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present> Search Strategy:

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1 exp Testosterone/aa, ad, ae, tu (9143)
2 Testosterone Congeners/ad, ae, tu (391)
3 exp Testosterone/ and Hormone Replacement Therapy/ (4361)
4 exp Androgens/ and Hormone Replacement Therapy/ (5792)
5 (testosteron* adj3 (replac* or substitut* or supplement* or therap* or treatment* or buccal or cream$1 or gel or gels or implant* or inject* or oral* or patch* or transdermal*)).tw. (20369)
6 (androgen* adj (replac* or substitut* or supplement* or therap* or treatment* or cream$1 or gel or gels or implant* or inject* or patch*)).tw. (6312)
7 (androgen* adj3 (buccal* or oral* or transdermal*)).tw. (632)
8 TRT.tw. (2125)
9 (testosterone adj (beta cyclopentylpropionate or cyclopentylpropionate or cipionate or cypionate or enanthate or enanthane or ethanate or heptonate or heptylate or oenanthate or undecanoate or undecylate or "17 undecylate")).tw. (2636)
10 ("8-Isotestosterone" or andriol or "andro 100" or "androgyn LA" or androderm or androfort or androgel or androlin or andronaq or andropatch or androsorb or androstenolone or androtardyl or androtest or androtop or andrusol or axiron).tw. (1095)
11 ("Bio-T-Gel" or Ciclosterone or "Cristerona T" or "Cristerone T" or CompleoTRT or "CP 601B" or Delatestryl or Depandro or Deposteron or Depostomead or Depo-Testosterone or Depotest or Depovirin or Depoviron or Delatestryl or Duratest or Durathate or Everone or "first-testosterone" or Fortesta or Rortigel or Hexanecarboxylate or Histerone or Homosteron* or Intrinsa or Jenasteron or LibiGel or Livensa or Malerone or Malogen or Malogex or Mertestate).tw. (492)
12 (Nasobol or Nebido or "Neo-Hombreol F" or "Neo-testis" or Neotestis or "NSC 9700" or Opterone or Oreton or "Oreton-F" or Orquisteron).tw. (292)
13 (Pantestone or Perandren or Percutacrine androgenique or Percutacrine androgine or Pertestis or Primotest or Primoteston or Relibra or Restandol or Sterotate or Striant or Sustanon$1 or "Sustason 250" or Synandrol).tw. (674)
14 (Teslen or "Testa-C" or Testamone or Testandrone or Testaqua or Testerone or Testex or Testiculosterone or Testim or Testo Enant or Testobase or Testoderm or Testogel or Testoject-50 or Testolin or Testoluton or Testopel or Testopropon or Testosteroid).tw. (691)
15 (Testostosterone or Testoviron or Testrin or Testro or Testrone or Theramex or Tostrelle or Testryl or Tostrex or Trans-Testosterone).tw. (604)
16 (UNII-3XMK78S47O or Undestor or Virilon or Virormone or Virosterone or Vogelxo).tw. (61)
17 or/1-16 (39453)
18 exp Animals/ not (exp Animals/ and Humans/) (8702141)
19 17 not 18 (25517)
20 (controlled clinical trial or randomized controlled trial).pt. (457659)
21 clinical trials as topic.sh. (169995)
22 (randomi#ed or randomly or RCT$1 or placebo*).tw. (1423548)
23 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (296647)
24 trial.ti. (292735)
25 or/20-24 (1829141)
26 19 and 25 (3594)
27 (comment or editorial or interview or letter or news).pt. (2802584)
28 26 not 27 (3546)
29 (control* adj2 trial*).tw. (323672)
30 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (73609)
31 (nRCT or nRCTs or non-RCT$1).tw. (647)
32 (control* adj3 ("before and after" or "before after")).tw. (6046)
33 time series.tw. (33994)
34 (pre- adj3 post-).tw. (110642)
35 (pretest adj3 posttest).tw. (6260)

36 (control* adj2 stud$3).tw. (346641)
37 Control Groups/ (74764)
38 (control$ adj2 group$1).tw. (752277)
39 or/29-38 (1509227)
40 19 and 39 (2115)
41 40 not 27 (2097)
42 exp Cohort Studies/ (1517558)
43 cohort$1.tw. (675350)
44 Retrospective Studies/ (837256)
45 (longitudinal or prospective or retrospective).tw. (1721897)
46 ((followup or follow-up) adj (study or studies)).tw. (89267)
47 Observational study.pt. (2469)
48 (observation$2 adj (study or studies)).tw. (111012)
49 ((population or population-based) adj (study or studies or analys#s)).tw. (26131)
50 ((multidimensional or multi-dimensional) adj (study or studies)).tw. (187)
51 Comparative Study.pt. (1676994)
52 ((comparative or comparison) adj (study or studies)).tw. (185742)
53 or/42-52 (4729450)
54 19 and 53 (3389)
55 54 not 27 (3352)
56 28 or 41 or 55 (6587
57 56 use prmz (3219) [ALL MEDLINE RECORDS]
58 28 use prmz (1720) [MEDLINE RCTS]
59 41 use prmz (845) [MEDLINE NON-RCTS]
60 55 use prmz (1837) [MEDLINE OBSERV]
61 androgen therapy/ (3539)
62 androgen deficiency/dt (507)
63 testosterone undecanoate/ (1591)
64 testosterone cipionate/ (871)
65 testosterone enantate/ (2439)
66 (testosteron* adj3 (replac* or substitut* or supplement* or therap* or treatment* or buccal or cream$1 or gel or gels or implant* or inject* or oral* or patch* or transdermal*)).tw. (20369)
67 (androgen* adj (replac* or substitut* or supplement* or therap* or treatment* or cream$1 or gel or gels or implant* or inject* or patch*)).tw. (6312)
68 (androgen* adj3 (buccal* or oral* or transdermal*)).tw. (632)
69 TRT.tw. (2125)
70 (testosterone adj (beta cyclopentylpropionate or cyclopentylpropionate or cipionate or cypionate or enanthate or enanthane or ethanate or heptonate or heptylate or oenanthate or undecanoate or undecylate or "17 undecylate")).tw. (2636)
71 ("8-Isotestosterone" or andriol or "andro 100" or "androgyn LA" or androderm or androfort or androgel or androlin or andronaq or andropatch or androsorb or androstenolone or androtardyl or androtest or androtop or andrusol or axiron).tw. (1095)
72 ("Bio-T-Gel" or Ciclosterone or "Cristerona T" or "Cristerone T" or CompleoTRT or "CP 601B" or Delatestryl or Depandro or Deposteron or Depostomead or Depo-Testosterone or Depotest or Depovirin or Depoviron or Delatestryl or Duratest or Durathate or Everone or "first-testosterone" or Fortesta or Rortigel or Hexanecarboxylate or Histerone or Homosteron* or Intrinsa or Jenasteron or LibiGel or Livensa or Malerone or Malogen or Malogex or Mertestate).tw. (492)
73 (Nasobol or Nebido or "Neo-Hombreol F" or "Neo-testis" or Neotestis or "NSC 9700" or Opterone or Oreton or "Oreton-F" or Orquisteron).tw. (292)
74 (Pantestone or Perandren or Percutacrine androgenique or Percutacrine androgine or Pertestis or Primotest or Primoteston or Relibra or Restandol or Sterotate or Striant or Sustanon$1 or "Sustason 250" or Synandrol).tw. (674)
75 (Teslen or "Testa-C" or Testamone or Testandrone or Testaqua or Testerone or Testex or Testiculosterone or Testim or Testo Enant or Testobase or Testoderm or Testogel or Testoject-50 or Testolin or Testoluton or Testopel or Testopropon or Testosteroid).tw. (691)
76 (Testostosterone or Testoviron or Testrin or Testro or Testrone or Theramex or Tostrelle or Testryl or Tostrex or Trans-Testosterone).tw. (604)
77 (UNII-3XMK78S47O or Undestor or Virilon or Virormone or Virosterone or Vogelxo).tw. (61)
78 or/61-77 (33099)
79 randomized controlled trial/ or controlled clinical trial/ (936519)
80 exp "clinical trial (topic)"/ (104828)
81 (randomi#ed or randomly or RCT$1 or placebo*).tw. (1423548)
82 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (296647)
83 trial.ti. (292735)
84 or/79-83 (1962147)
85 78 and 84 (4042)
86 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (37422531)
87 exp humans/ or exp human experimentation/ or exp human experiment/ (28425359)
88 86 not 87 (8998814)
89 85 not 88 (3544)
90 (letter or editorial).pt. (2492646)
91 89 not 90 (3515)

92 (control* adj2 trial*).tw. (323672)
93 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (73609)
94 (nRCT or nRCTs or non-RCT$1).tw. (647)
95 (control* adj3 ("before and after" or "before after")).tw. (6046)
96 time series analysis/ (13996)
97 time series.tw. (33994)
98 pretest posttest control group design/ (202)
99 (pre- adj3 post-).tw. (110642)
100 (pretest adj3 posttest).tw. (6260)
101 controlled study/ (4336835)
102 (control* adj2 stud$3).tw. (346641)
103 control group/ (74764)
104 (control* adj2 group$1).tw. (752277)
105 or/92-104 (5430128)
106 78 and 105 (7057)
107 106 not 88 (3849)
108 107 not 90 (3833)
109 cohort analysis/ (334727)
110 cohort$1.tw. (675350)
111 retrospective study/ (837256)
112 longitudinal study/ (153245)
113 prospective study/ (618128)
114 (longitudinal or prospective or retrospective).tw. (1721897)
115 follow up/ (824941)
116 ((followup or follow-up) adj (study or studies)).tw. (89267)
117 observational study/ (58475)
118 (observation$2 adj (study or studies)).tw. (111012)
119 population research/ (68859)
120 ((population or population-based) adj (study or studies or analys#s)).tw. (26131)
121 ((multidimensional or multi-dimensional) adj (study or studies)).tw. (187)
122 exp comparative study/ (2694962)
123 ((comparative or comparison) adj (study or studies)).tw. (185742)
124 or/109-123 (5973302)
125 78 and 124 (4650)
126 125 not 88 (3667)
127 126 not 90 (3625)
128 91 or 108 or 127 (7409)
129 128 use emczd (5052) [ALL EMBASE RECORDS]
130 91 use emczd (2221) [EMBASE RCTS]
131 108 use emczd (3091) [EMBASE NON-RCTS]
132 127 use emczd (2341) [EMBASE OBSERV]
133 58 or 130 (3941) [MEDLINE/EMBASE RCTS]
134 remove duplicates from 133 (2771) [UNIQUE RCTS]
135 134 use prmz (1666) [MEDLINE UNIQUE RCTS]
136 134 use emczd (1105) [EMBASE UNIQUE RCTS]
137 59 or 131 (3936) [MEDLINE/EMBASE NON-RCTS]
138 137 not 133 (1817) [OVERLAP REMOVED]
139 remove duplicates from 138 (1633) [UNIQUE NON-RCTS]
140 139 use prmz (264) [MEDLINE UNIQUE NON-RCTS]
141 139 use emczd (1369) [EMBASE UNIQUE NON-RCTS]
142 60 or 132 (4178) [MEDLINE/EMBASE OBSERV]
143 142 not (133 or 137) (2513) [OVERLAP REMOVED]
144 remove duplicates from 143 (2170) [UNIQUE OBSERV]
145 144 use prmz (1216) [MEDLINE UNIQUE OBSERV STUDIES]
146 144 use emczd (954) [EMBASE UNIQUE OBSERV STUDIES]
147 134 or 139 or 144 (6574) [UNIQUE RECORDS – ALL STUDY TYPES]

eAppendix 2: Scales represented in the analysis of data for each outcome

Qualtiy of life	Aging Males' Symptoms
	Minnesota Living with Heart Failure Questionnaire
	Quality of Life Specific to Male Erection Difficulties
	International Prostate Symptoms Score Quality of Life
	Quality of Life Enjoyment and Satisfaction Questionnaire
	Questions on Life Satisfaction, health subscale
	Health Related Quality of Life, sexual function domainSF-36 (total score)
Depression	Hospital Anxiety and Depression Scale
	Beck's Depression Inventory
	General Well-Being Index, depressed mood dimension
	Geriatric Depression Scale
	Hamilton Depression Scale
Libido	International Index of Erectile Function (sexual desire domain)
	Men's Sexual Health Questionnaire (sexual desire domain)
	Partial Androgen Deficiency in Aging Men (PADAM) Questionnaire
	Psychosexual Daily Questionnaire
Erectile function	International Index of Erectile Function (IIEF-5 or erectile function domain of IIEF-15)

eAppendix 3: Included studies*

*The list of excluded studies is available from the authors on request.

Note: studies were not evaluated for inclusion on the basis reported outcomes.

1. Agarwal PK, Oefelein MG. Testosterone replacement therapy after primary treatment for prostate cancer. *J Urol.* 2005; 173: 533–6.
2. Agledahl I, Brodin E, Svartberg J, et al. Impact of long-term testosterone treatment on plasma levels of free TFPI and TF-induced thrombin generation ex vivo in elderly men with low testosterone levels. *Thrombo Haemostasis*. 2009; 102: 945.
3. Agledahl I, Hansen JB, Svartberg J. Impact of testosterone treatment on postprandial triglyceride metabolism in elderly men with subnormal testosterone levels. *Scand J Clin Lab Invest* 2008; 68: 641.
4. Alamir MA, Ellenberg SS, Swerdloff RS, et al. The Cardiovascular Trial of the Testosterone Trials: Rationale, design, and baseline data of a clinical trial using computed tomographic imaging to assess the progression of coronary atherosclerosis. *Coronary Artery Disease.* 2016;27:95.
5. Amory JK, Watts NB, Easley KA, et al. Exogenous testosterone or testosterone with finasteride increases bone mineral density in older men with low serum testosterone. *J Clin Endocrinol Metab* 2004; 89: 503–10.
6. Andrade ES, Jr., Clapauch R, Buksman S. Short term testosterone replacement therapy improves libido and body composition. *Arq Bras Endocrinol Metabol* 2009;53:996–1004.
7. Arafa M, Zohdy W, Aboulsoud S, et al. Prevalence of late-onset hypogonadism in men with type 2 diabetes mellitus. *Andrologia* 2012; 44: 756.
8. Arver S, Sinha-Hikim I, Beall G, Guerrero M, Shen R, Bhasin S. Serum dihydrotestosterone and testosterone concentrations in human immunodeficiency virus-infected men with and without weight loss. *J Androl* 1999; 20: 611–8.
9. Atkinson RA, Srinivas-Shankar U, Roberts SA, et al. Effects of testosterone on skeletal muscle architecture in intermediate-frail and frail elderly men. *J Gerontol A Biol Sci Med Sci* 2010; 65: 1215.
10. Aversa A, Bruzziches R, Francomano D, et al. Effects of testosterone undecanoate on cardiovascular risk factors and atherosclerosis in middle-aged men with late-onset hypogonadism and metabolic syndrome: results from a 24-month, randomized, double-blind, placebo-controlled study. *J Sex Med* 2010; 7: 3495.
11. Aversa A, Bruzziches R, Francomano D, Spera G, Lenzi A. Efficacy and safety of two different testosterone undecanoate formulations in hypogonadal men with metabolic syndrome. *J Endocrinol Invest* 2010; 33: 776–3.
12. Aversa A,Bruzziches R, Francomano D, et al. Effects of long-acting testosterone undecanoate on bone mineral density in middle-aged men with late-onset hypogonadism and metabolic syndrome: Results from a 36 months controlled study. *Aging Male* 2012; 15: 96.
13. Aydogdu A, Bolu E, Sonmez A, et al. Effects of three different medications on metabolic parameters and testicular volume in patients with hypogonadotropic hypogonadism: 3-year experience. *Clin Endocrinol* 2013; 79: 243–51.
14. Bachman E, Travison TG, Basaria S, et al. Testosterone induces erythrocytosis via increased erythropoietin and suppressed hepcidin: evidence for a new erythropoietin/hemoglobin set point. *J Gerontol A Biol Sci Med Sci* 2014; 69: 725–735.
15. Basaria S, Coviello AD, Travison TG, et al. Adverse events associated with testosterone administration. *N Engl J Med* 2010; 363: 109–22.
16. Basaria S, Davda MN, Travison TG, Ulloor J, Singh R, Bhasin S. Risk factors associated with cardiovascular events during testosterone administration in older men with mobility limitation. *J Gerontol A Biol Sci Med Sci* 2013; 68: 153–160.
17. Basaria S, Harman SM, Travison TG, et al. Effects of Testosterone Administration for 3 Years on Subclinical Atherosclerosis Progression in Older Men With Low or Low-Normal Testosterone Levels: A Randomized Clinical Trial. *JAMA : the journal of the American Medical Association.* 2015;314:570.
18. Basaria S, Travison TG, Alford D, et al. Effects of testosterone replacement in men with opioid-induced androgen deficiency: a randomized controlled trial. *Pain.* 2015;156:280.

19. Basurto L, Zarate A, Gomez R, Vargas C, Saucedo R, Galvan R. Effect of testosterone therapy on lumbar spine and hip mineral density in elderly men. *Aging Male* 2008; 11: 140–5.
20. Beggs LA, Yarrow JF, Conover CF, et al. Testosterone alters iron metabolism and stimulates red blood cell production independently of dihydrotestosterone. *Am J Physiol Endocrinol Metab* 2014; 307: E456–E461.
21. Behre HM, Tammela TL, Arver S., et al. A randomized, double-blind, placebo-controlled trial of testosterone gel on body composition and health-related quality-of-life in men with hypogonadal to low-normal levels of serum testosterone and symptoms of androgen deficiency over 6 months with 12 months open-label follow-up. *Aging Male* 2012; 15: 198.
22. Bhasin S, Storer TW, Asbel-Sethi N, et al. Effects of testosterone replacement with a nongenital, transdermal system, Androderm, in human immunodeficiency virus-infected men with low testosterone levels. *J Clin Endocrinol Metab* 1998; 83: 3155–62.
23. Bhasin S, Storer TW, Javanbakht M, et al. Testosterone replacement and resistance exercise in HIV-infected men with weight loss and low testosterone levels. *JAMA* 2000; 283: 763–70.
24. Black AM, Day AG, Morales A. The reliability of clinical and biochemical assessment in symptomatic late-onset hypogonadism: Can a case be made for a 3-month therapeutic trial? *BJU International* 2004; 94: 1066–70.
25. Blick G. Optimal diagnostic measures and thresholds for hypogonadism in men with HIV/AIDS: comparison between 2 transdermal testosterone replacement therapy gels. *Postgrad.Med* 2013; 125: 30–9.
26. Borst SE, Yarrow JF, Conover CF, et al. Musculoskeletal and prostate effects of combined testosterone and finasteride administration in older hypogonadal men: a randomized, controlled trial. *Am J Physiol Endocrinol Metab* 2014; 306: E433–E442.
27. Borst SE, Yarrow JF, Fernandez C, et al. Cognitive effects of testosterone and finasteride administration in older Hypogonadal men. *Clin Interv Aging.* 2014; 9: 1327–33.
28. Boyanov MA, Boneva Z, Christov VG. Testosterone supplementation in men with type 2 diabetes, visceral obesity and partial androgen deficiency. *Aging Male* 2003; 6: 1–7.
29. Brock G, Heiselman D, Maggi M, Kim SW, Rodr JM. Effect of Testosterone Solution 2% on Testosterone Concentration, Sex Drive and Energy in Hypogonadal Men: Results of a Placebo Controlled Study. *J Urol.* 2016;195:699.
30. Brockenbrough AT, Dittrich MO, Page ST, Smith T, Stivelman JC, Bremner WJ. Transdermal androgen therapy to augment EPO in the treatment of anemia of chronic renal disease. *Am J Kidney Dis* 2006; 47: 251–62.
31. Budoff MJ, Ellenberg SS, Lewis CE, et al. Testosterone Treatment and Coronary Artery Plaque Volume in Older Men With Low Testosterone. *JAMA : the journal of the American Medical Association.* 2017;317:708.
32. Buisson J. Effects of testosterone supplementation on sexual function in elderly men: Results of a six month randomised, placebo controlled study. *Cahiers de l'Annee Gerontologique* 2010; 2: 144–6.
33. Burnett AL, Kan-Dobrosky N, Miller MG. Testosterone replacement with 1% testosterone gel and priapism: no definite risk relationship. *J Sex Med* 2013; 10: 1151–61.
34. Caminiti G, Volterrani M, Iellamo F, et al. Effect of long-acting testosterone treatment on functional exercise capacity, skeletal muscle performance, insulin resistance, and baroreflex sensitivity in elderly patients with chronic heart failure a double-blind, placebo-controlled, randomized study. *J Am College Cardiol* 2009; 54: 919.
35. Cavallini G, Biagiotti G, Giudice C. Association between Peyronie disease and low serum testosterone levels: detection and therapeutic considerations. *J Androl* 2012; 33: 381.
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eAppendix 4: Characteristics of the included RCTs and NRS

eTable 1: Characteristics of included RCTs that reported at least 1 outcome of interest

Author, year, page (companion publications)	Population*	Duration	Groups (no. randomized)	Age, yr, mean (SD);	Baseline Total T, mean (SD), nmol/L	Industry funding
Dias 2016, p. 1865 (Dias 2017 p.143; Dias 2016, p. 33; Dias 2017, p. 31)	Older men with low testosterone	12 mo	1% Gel, 50 mg/d (16) Placebo (13)	72 (SEM 1) 72 (SEM 1)	10.4 (1.9) 10.5 (2.1)	No
Chillaron 2016, p. 849	T1D	22 wk	IM TU 1000 mg/10 wk (6) Placebo (7)	47.9 (7.3) 45.2 (11.7)	12.4 (3.5) 9.9 (4.5)	Yes
Brock 2016, p. 699 (Maggi 2017, p. 1220)	≥ 1 symptom of testosterone deficiency	12 wk	2% solution, 60 mg/d (358) Placebo (357)	54.7 (10.6) 55.9 (11.4)	7.0 (2.3) 7.0 (2.3)	Yes
Dhindsa 2016, p. 82	T2DM	24 wk	IM TC, 250 mg/2wk (22) Placebo (22)	54.6 (7.9) (NR by group)	8.7 (2.8) (NR by group)	No
Konaka 2016, p. 25 (Shigehara 2017, p. 1; Shigehara 2015, p. 169)	Late onset hypogonadism	52 wk	IM TE, 250 mg/4 wk (169) No treatment (165)	65.7 (9) 67.6 (9.4)	Free T 7.1 (3.2) 6.7 (3.5) pg/ml	No
Magnussen 2016, p. 980	T2DM	24 wk	1% gel, 50 mg/d (22) Placebo (21)	61 (6) 59 (6)	7.1 (95%CI 6.6-11.9) 9.4 (95%CI 8.1-12.5)	Yes
Ng Tang Fui 2016, p. 153 (Ng Tang Fui 2017, p. 420)	BMI ≥ 30	56 wk	IM TU, 1000 mg/10 wk (49) Placebo (51)	54.3 (IQR 47.3-59.8) 52.8 (IQR47.6-60.1)	8.2 (2.5) 8.4 (2.3)	Yes
Sinclair 2016, p. 906	Cirrhosis	54 wk	IM TU, 1000 mg/12 wk (50) Placebo (51)	55.5 (IQR 52-60) 54.0 (IQR 50-59)	9.3 (IQR 3.9-17) 9.1 (IQR 2.7-12.7)	Yes
Snyder 2016 p. 611† (Cunningham 2016, p. 3096; Snyder 2017, p. 471; Roy 2017, p. 480; Resnick 2017, p. 717; Cunningham 2015, p. 1146; Abd Alamir 2016, p. 95; Swerdloff 2015,	Older men with decreased libido or sexual function (Sexual function trial); limited mobility (Physical function trial); low vitality (Vitality trial)	12 mo	1% gel, 50 mg/d (395) Placebo (395)	72.1 (5.7) 72.3 (5.8)	8.0 (2.2) 8.2 (2.3)	Mix

p. 3280; Budoff 2017, p. 708)						
Basaria 2015, p. 570 (Storer 2017, p. 583)	Older men	3 yr	1% gel, 75 mg/d (156) Placebo (152)	66.9 (5.0) 68.3 (5.3)	10.7 (2.2) 10.7 (2.3)	Yes
Basaria 2015, p. 280 (Huang 2016, p. 232)	Opioid-induced hypogonadism	12 wk	1% gel, 50 mg/d (43) Placebo (41)	48 (9) 50 (6)	8.2 (3.4) 7.7 (3.0)	Yes
Cherrier 2015, p. 421	Mild cognitive impairment	6 mo	Gel, 50-100 mg/d (10) Placebo (12)	70.5 (8.2)	10.7 (3.2) 9.8 (2.7)	Mix
Paduch 2015, p.2956	Ejaculatory dysfunction	16 wk	2% solution, 60 mg/d (36) Placebo (40)	48.4 (9.8) 52.7 (9.3)	7.4 (1.9) 7.7 (1.8)	Yes
Borst 2014, p. E433	Hypogonadal	12 mo	Placebo (16) IM TE, 125 mg/wk (14)	70.8 (9.7) 69.2 (8.0)	8.5 (10.1) 9.2 (11.9)	Mix
Gianatti 2014, p. 2098 (Gianatti 2014, p. 3821; Gianatti 2016, p. 55)	Type 2 diabetes	40 wk	Placebo (43) IM TU, 1000 mg/12 wk (45)	62 (7.4) 62 (8.1)	8.5 (2.8) 8.7 (3.0)	Yes
Hackett 2013, p.1891 (Hackett 2013, p. 1612, Hackett 2014)	T2DM and symptoms of hypogonadism	30 wk	Placebo (102) IM TU, 1000 mg/12 wk (97)	62.0 (9.3) 61.2 (10.5)	8.9 (3.8) 9.2 (3.1)	Yes
Wang 2013, p. 1	Osteoporosis	24 mo	Placebo (62) Oral TU, 20 mg/d (62) Oral TU, 40 mg/d (62)	68.0 (4.8) 68.4 (5.5) 68.1 (5.4)	7.6 (0.7) 7.6 (0.9) 7.4 (0.8)	No
Behre 2012, p. 198	AMS score >36	6 mo	Placebo (179) 1% gel, 50 mg/d (183)	62.1 (6.3) 61.9 (6.6)	10.6 (2.6) 10.4 (2.6)	Yes
Spitzer 2012, p. 681 (Spitzer 2013)	Erectile dysfunction	14 wk	Placebo (70) 1% gel, 100 mg/d (70)	54.6 (8.5) 55.1 (8.3)	8.8 (2.4) 8.6 (2.2)	No
Stout 2012, p. 893	Chronic heart failure	12 wk	Placebo (20) Sustanon,‡ 100 mg/2 wk (20)	65.9 (8.8) 68.3 (5.3)	11.2 (2.6) 10.4 (2.7)	No
Zhang 2012, p. 3806	Positive score on ADAM questionnaire	6 mo	Vitamin E/C (80) Oral TU, 120 or 160 mg/d (based on T level at baseline)(80)	61.1 (7.1) 59.4 (6.3)	7.7 (0.8) 8.0 (0.7)	No
Ho 2011, p. 260 (Tan 2013, Tong 2012)	At least mild AMS symptoms	42 wk	Placebo (60) IM TU, 1000 mg/12 wk (60)	53.0 (8.2) 53.4 (7.4)	8.9 (2) 9.1 (1.8)	Yes

Jones 2011, p. 828 (Stanworth 2014)	MetS or T2DM with at least 2 symptoms of hypogonadism	12 mo	Placebo (112) 2% gel, 60 mg/d (108)	59.9 (9.4) 59.9 (9.1)	9.5 (3.3) 9.2 (2.6)	Yes
Kaufman 2011, p. 2079	"otherwise healthy"	6 mo	Placebo (40) 1.62% gel, 40.5 mg/d (234)	55.5 (10.3) 53.6 (9.5)	10.2 (NR) 9.8 (NR)	Yes
Sheffield-Moore 2011, p. E1831 (Fitts 2015, p. E223)	Community-dwelling men	5 mo	Placebo (8) IM TE, 100 mg/wk (8)	65 (3) 73 (8)	11.8 (2.9) 11.9(2.9)	No
Shigehara 2011, p. 53	Benign prostate hypertrophy	12 mo	No treatment (26) IM TE, 250 mg/4 wk (26)	68.9 (9.1) 72 (6.5)	Free T 6.7 (1.9) pg/ml 7.0 (1.7) pg/ml	NR
Aversa 2010, p. 776	MetS or T2DM	6 mo	Placebo (10) Oral TU 160 mg/d (10) IM TU 1000 mg/12 wk (32)	55 (5) 57 (8) 58 (10)	11.1 (NR by group)	NR
Aversa 2010, p. 3495	MetS or T2DM	12 mo	Placebo (10) IM TU, 1000 mg/12wk (40)	57 (8) 58 (10)	9.0 (1.7) 8.33 (2.4)	NR
Basaria 2010, p. 109 (Bachman 2014, Huang 2013, Basaria 2013, Travison 2011; Storer 2016)	Limited mobility	6 mo	Placebo (103) 1% gel, 100 mg/d (106)	74 (5) 74 (6)	8.2 (2.3) 8.7 (2.0)	No
Kalinchenko 2010, p. 602 (Giltay 2010)	MetS	30 wk	Placebo (71) IM TU, 1000 mg/12wk (113)	52.8 (9.67) 51.6 (9.76)	7.5 (5.2) 6.7 (3.0)	Yes
Kenny 2010, p. 1134	Low bone mass and frailty	12–24 mo	Placebo (62) 1% gel, 5 mg/d (69)	76.3 (8.0) 77.9 (7.3)	14.5 (6.7) 13.2 (6.2)	Mix
Srinivas-Shankar 2010, p. 639 (O'Connell 2010, Atkinson 2010)	Intermediate-frail and frail	6 mo	Placebo (136) 1% gel, 50 mg/d (138)	73.9 (6.4) 73.7 (5.7)	10.9 (3.1) 11 (3.2)	Yes
Caminiti 2009, p. 919 (Schwartz 2011)	Chronic heart failure	12 wk	Placebo (35) IM TU, 1000 mg/6 wk (35)	69 (66–74) 71 (67–76)	7.3 (7.3) 8.0 (6.2)	No
Chiang 2009, p. 467	Hypogonadal	3 mo	Placebo (20) 1% gel, 50 mg/d (20)	NR	NR	NR
Emmelot-Vonk, 2009, p. 129 (Emmelot-Vonk	Moderately low T levels	26 wk	Placebo (117) Oral TU, 160 mg/d (120)	67.4 (4.9) 67.1 (5.0)	10.4 (1.9) 11.0 (1.9)	No

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2008, Nakhai-Pour 2007, Buisson 2010)						
Heufelder 2009, p. 726	MetS and T2DM	52 wk	Placebo (16) 1% gel, 50 mg/d (16)	55.9 (6) 57.3 (5.6)	10.4 (0.8) 10.5 (0.8)	Yes
Hohl 2009, p. 989	High AMS score	12 or 14 wk	IM TU, 1000 mg/6 wk (10) IM TC, 200 mg/4wk (11) Durateston, IM, 250 mg/4wk (11)	59.6 (8.9) 59.6 (7.1) 60.4 (8.8)	9.9 (1.1) 10.1 (1.1) 9.9 (1.5)	No
Mathur 2009, p. 443	Chronic angina pectoris	12 mo	Placebo (7) IM TU, 1000 mg/12 wk (8)	67.8 (7.9) 62.1 (5.2)	10.1 (2.8) 9.8 (1.9)	Yes
Morales 2009, p. 104	Sexual dysfunction	4 mo	Placebo (29) Oral TU, 160 mg/d (29)	60.2 (9.6) 59.0 (10.6)	10.0 (5.5) 10.2 (4.9)	Yes
Shores 2009, p. 1009	Dysthymia or minor depression	12 wk	Placebo (16) 1% gel, 75 mg/d (17)	61.7 (7.0) 57.1 (5.7)	9.3 (3.4) 10.1 (3.7)	Mix
Agledahl 2008, p. 641	Subnormal total T	52 wk	Placebo (13) IM TU, 1000 mg/12 wk (14)	69.3 (5.0) 68.9 (5.4)	8.2 (2.4) 8.5 (1.7)	Mix
Basurto 2008, p. 140	Low total T	12 mo	Placebo (23) IM TE, 250 mg/3wk (25)	63.1 (7.7) 63.2 (8.5)	10.8 (1.3) 10.4 (1.1)	No
Raynaud 2008, p. 168	Hypogonadal	6 mo	Patch, 4.8 mg/d(188) IM TE, 250 mg/3 wk (36)	42.0 (12.7) 40.7 (10.5)	4.6 (3.2 5.1 (3.3)	Yes
Svartberg 2008, p. 378	NR	12 mo	Placebo (19) IM TU, 1000 mg/12 wk (19)	69 (5) 69 (5)	8.2 (2.1) 8.4 (1.7)	Mix
Chiang 2007, p. 411	Hypogonadal	3 mo	Placebo (20) 1% gel, 50 mg/d (20)	56.1 (14.6) 47.9 (17.0)	9.1 (6.9) 7.4 (5.6)	Yes
Brockenbrough 2006, p. 251	Hemodialysis-dependent end-stage renal disease	6 mo	Placebo (21) 1% gel, 100 mg/d (19)	53.0 (17.2) 58.9 (14.9)	7.0 (3.0) 7.6 (2.2)	Yes
Marks 2006, p. 2351	Symptoms of LOH	6 mo	Placebo (22) IM TE, 150 mg/2wk (22)	68 (NR) 70 (NR)	8.7 (1.6) 7.7 (1.4)	Mix
Merza 2006, p. 381	Sexual dysfunction	6 mo	Placebo (19) Patch, 5 mg/d (20)	59.7 (10.2) 63.0 (9.0)	7.5 (2.5) 8.4 (3.3)	Yes
Kuhnert 2005, p. 317	Primary, secondary, LOH	24 wk	Patch, 5 mg/d (52) 2.5%, gel, 125 mg/d (56) 2.5%, scrotal gel, 25 mg/d (54)	53 (IQR 16) 52.2 (IQR 22.5) 50 (IQR 21)	NR	Yes

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	and symptoms of T deficiency					
Orengo 2005, p. 20	Treatment-resistant depression	12 wk	Placebo (5) 1% gel, 50 mg/d (7)	63 (8.5) (NR by group)	8.9 (1.7) 10.2 (2.3)	No
Amory 2004, p. 503 (Page 2005, Vaughan 2007)	T below the range of normal for young adult men	36 mo	Placebo (24) IM TE 200 mg/2wk (24)	71 (4) 71 (4)	10.1 (2.1) 9.9 (1.6)	No
Cavallini 2004, p. 641	Symptoms of androgen decline	6 mo	Placebo (45) Oral TU, 160 mg/d (40)	63 (NR) 64 (NR)	10.5 (2.1) 9.9 (1.8)	No
Schubert 2004, p. 5429 (Jockenhovel 2009, Jockenhovel 2009, Minnemann 2008)	Primary or secondary hypogonadism	30 wk	IM TU, 1000 mg/9 wk (20) IM TE, 250 mg/3 wk (20)	41.1 (13.4) 36.3 (12.3)	3.9 (4.4) 2.7 (2.3)	Mix
Shabsigh 2004, p. 658 (Burnett 2013, Wang 2001, Swerdloff 2000)	Erectile dysfunction not responsive to sildenafil	12 wk	Placebo (36) 1% gel, 50 mg/d (39)	59.1 (9.4) 56.8 (10.2)	65% had T < 10.4 (NR by group)	Yes
Boyanov 2003, p. 1	T2DM, obesity, and "symptoms of andropause or erectile dysfunction"	3 mo	No treatment (24) Oral TU, 120 mg/d (24)	All: 57.5 (4.8) (NR by group)	10.76 (11.20) 9.56 (2.33)	NR
McNicholas 2003, p. 69	≥ 1 symptoms of "low T"	90 d	Patch, 5 mg/d (68) 1% gel, 50 mg/d (68) 1% gel, 100 mg/d (72)	57.9 (10.2) 59.0 (9.5) 56.7 (10.3)	7.90 (2.2) 7.95 (2.2) 7.92 (2.4)	Yes
Steidle 2003, p. 2673 (Seftel 2004)	≥ 1 symptoms of "low T"	90 d	Placebo (99) Patch, 5 mg/d (102) 1% gel, 50 mg/d (99) 1% gel, 100 mg/d (106)	56.8 (10.8) 60.5 (9.7) 58.1 (9.7) 56.8 (10.6)	7.9 (2.8) 8.3 (2.4) 8.1 (2.0) 8.1 (2.1)	Yes
Tan 2003, p. 13	Alzheimer's disease	12 mo	Placebo (5) IM TE, 200mg/2wk (5)	68.9 (NR) 72.4 (NR)	NR 3.6 (NR)	No
Ferrando 2002, p. 358 (Ferrando 2003)	"Healthy older men"	6 mo	Placebo (5) IM TE 50–400 mg/wk (7)	67 (6.7) 68 (7.9)	9.8 (4.3) 12.4 (4.4)	No

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Kang 2002, p. 862	Coronary artery disease	12 wk	Placebo 17) Oral TU, 160 mg/d (18)	58 (9) 57 (7)	Free T, 13.8 (1.8) pg/ml 9.9 (3.1) pg/ml	NR
Simon 2001, p. 2149	Healthy adult men	3 mo	Placebo (6) Gel, 125 mg/d (6)	55.4 (3.6) 52.8 (4.2)	9.4 (1.0) 8.3 (0.3)	NR
Bhasin 2000, p. 763	HIV-infected with weight loss	16 wk	Placebo (14) IM TE, 100 mg/wk (17)	41.8 (9.4) 40.8 (4.9)	6.1 (2.9) 7.1 (3.0)	No
Wang 2000, p. 2839	Primary, secondary or LOH	90 d	Patch, 5 mg/d (76) 1% gel, 50 mg/d (76) 1% gel, 100 mg/d (78)	51.1 (NR) 51.3 (NR) 51.0 (NR)	8.2 (4.8) 8.2 (4.6) 8.6 (4.8)	Mix
Clague 1999, p. 261	Community-living	3 mo	Placebo (7) IM TE, 200 mg/2wk (7)	65.3 (1.8) 68.1 (6.6)	11.6 (0.9) 11.3 (1.7)	No
Dobs 1999, p. 3469	Receiving TRT for at least 3 mo	24 wk	Patch, 5 mg/d (33) IM TE, 200 mg/2wk (33)	44.3 (11.1) 44.9 (11.6)	5.8 (2.7) 6.3 (3.3)	Mix
Bhasin 1998, p. 3155 (Arver 1999)	HIV	12 wk	Placebo (21) Patch, 5 mg/d (20)	NR	7.3 (2.9) 9.0 (1.7)	Mix
Grinspoon 1998, p. 18 (Grinspoon 2000)	AIDS wasting syndrome	6 mo	Placebo (26) IM TE, 300 mg/3wk (26)	44 (9) 40 (7)	10.1 (6.4) 11.3 (5.4)	No
Jockenhovel 1997, p. 2510	Primary or secondary androgen deficiency	12 wk	IM TE, 250 mg/3 wk (10) Pellets, 1200 mg (12)	30.0 (7.3) 36.3 (11.1)	1.6 (1.3) 1.9 (1.1)	NR
Jockenhovel 1997, p. 293 (Jockenhovel 1999, Schubert 2001)	Primary or secondary androgen deficiency	210 d	Oral TU, 160 mg/d (13) IM TE, 250 mg/3wk (15) Pellets, 1200 mg (15)	34.5 (14.1) 31.8 (10.1) 35.8 (10.4)	2.9 (1.4) 2.3 (2.3) 2.7 (1.5)	NR
Sih 1997, p. 1661	Community-dwelling healthy men	12 mo	Placebo (15) IM TC, 200 mg/2wk (17)	68 (6) 65 (7)	8.1 (0.7) 10.2 (0.9)	NR

Note: ADAM = Androgen Deficiency of the Aging Male, AMS = Aging Males' Symptoms [scale], CI = confidence interval, IM = intramuscular, IQR = interquartile range, LOH = late onset hypogonadism, MetS = metabolic syndrome, NR = not reported, SD = standard deviation, T = testosterone, T1D = type 1 diabetes, T2DM = type 2 diabetes mellitus, TC = testosterone cypionate, TE = testosterone enanthate, TRT = testosterone replacement therapy, TU = testosterone undecanoate.

*All RCTs involved men that were either described as hypogonadal and met the cut-off for hypogonadism (total T < 12 nmol/L or free T < 225 pmol/L) or reported total or free T below these cut-off points.

†The Testosterone Trials were a coordinated set of seven trials. In order to enroll, participants had to qualify for at least one of the Sexual Function Trial, Physical Function Trial, or the Vitality Trial (NCT00799617).

‡Blend of testosterone propionate, testosterone phenylpropionate, testosterone isocaproate, and testosterone decanoate.

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eTable 2: Characteristics of included non-randomized studies that reported at least one outcome of interest

Study	Population*	Duration	Group (no. in group)	Age, yr, mean (SD)	Baseline total T, mean (SD), nmol/L†	Industry funding
Retrospective cohort						
Cheetham 2017, p. 491	≥ 40 yr with documented androgen deficiency	Follow-up: 4.4 years (mean)	TRT (injection, oral, topical), dose NR (8,808) Never TRT (35,527)	58.4 (NR) 59.8 (NR)	TRT group: 7.4 (IQR 5.5-8.8)**	No
Layton 2015, p. 1187	New users of TRT‡		Gel (114,918) Injection (111,354) Patch (9,906)	Range: 52.4 (15.1) to 72.7 (6.7)§	NR††	No
Pastuszak 2015, p. 165	New TRT users or had been off TRT for ≥ 3 or mo	26.2 (10.6) 29.8 (8.8) 28.2 (8.6) mo	Gel (1% 50–100 mg/d and 1.62% 20.25–80.1 mg/d) (47) IM TE or TC, 100–200mg/wk (57) Pellets, 75 mg/3–6 mo (74)	54.1 (9.8) 42.5 (12.3) 53.8 (13.0)	10.4 (3.1) 10.6 (5.7) 9.3 (5.8)	No
Ramasamy 2016	≥ 65 yr and ≥3 hypogonadal symptoms	3.4-3.8 yr	TRT, dose NR (153) No treatment (64)	74 (6.3) 75(6)	NR	NR
Aydogdu 2013, p. 243	IHH	24 wk	Sustanon, ¶ IM 250 mg/3wk (28) 1% gel, 50 mg/d (24)	20.9 (1.4) 21.3 (1.6)	0.9 (0.6) 1.4 (1.3)	No
Vigen 2013, p. 1829	Men who underwent coronary angiography at a VA medical centre	Follow-up: 840 d (mean)	TRT, dose NR (1223) No treatment (7486)	60.6 (7.6) 63.8 (9.0 yr)	6.1 (2.2) 7.2 (2.6)	NR
Shores 2012, p. 2050	> 40 yr treated at a VA medical center	20.2 (16.7) mo	TRT, dose NR (398) No treatment (633)	62.1 (10.6)	5.6 (2.2) 6.7 (1.9)	No
Rhoden 2006, p. 201	Hypogonadal men with negative prostate biopsy prior to initiation of TRT	12 mo	IM TRT, dose NR (33) 1% gel, dose NR (25)	58.3	10.3 (5.4) 10.2 (3.1)	No
Guay 2000, p. 132	Men with ED and primary or secondary hypogonadism	2-3 mo	IM TE, 200–300 mg/2-3 wk (25) Patch, 5 mg/d (16)	40–80	Free T: 8.1–9.7 pg/ml	NR
Hajjar 1997, p. 3793	Elderly men	24 mo	IM TE or TC, IM 200 mg/2 wk (45) No treatment (27)	71.8 (SE 1.7) 69.9 (SE 1.9)	10.8 (4.7) 9.6 (3.8)	NR
Prospective cohort						

Debruyne 2017, p. 216	≥18 years with a diagnosis of hypogonadism	36 mo	TRT, dose NR (750) No TRT (249)	58.9 (10.3) 59.7 (11.1)	8.3 (3.9) 9.4 (3.7)	Yes
Traish 2016, p. 1	Symptoms of hypogonadism	Up to 8 yr	IM TU, 1000 mg/12wk (360) No TRT (296)	57.4 (7.3) 64.8 (4.3)	9.8 (1.3) 9.6 (1.2)	Yes
Yassin 2017, p. 1	Treated or untreated hypogonadal men	6 yr	TRT, dose NR (42) No treatment (162)	61.3 (4.7)	≤ 12.1 7.1 (2.3)	NR
Jung 2016, p. 194	Symptoms of hypogonadism	8 mo	TU, 1000 mg/3 mo + lifestyle modification (54) Lifestyle modification (52)	56.7 (12.6) 57.8 (11.4)	8.7 (2.1) 9 (2.4)	No
Francomano 2014, p. 401	Severely obese men (mean BMI 42) with ≥ symptoms of hypogonadism	54 wk	DPE (12) DPE + IM TU, 1000 mg/12 wk (12)	53 (8) 56 (9)	8.2 (1.8) 8.5 (1.8)	NR
Blick 2013, p. 30	HIV/AIDS	12 mo	1% gel (Androgel), 50 mg/d (92) 1% gel (Testim), 50 mg/d (75)	49.5 (8.1)	13.9 (5.5)‡‡ 13.7 (7.2)	Yes
Aversa 2012, p. 96	Middle-aged men with LOH and MetS	36 mo	IM TU, 1000 mg/12 wk (40) No treatment (20)	58 (10) 57 (8)	8.3 (2.4)	NR
Dean 2005, p. 87	21–81 yr	Up to 12 mo	1% gel, 50 mg/d (NR) 1% gel, 100 mg/d (NR)	58.5 (10.0)	8.1 (2.1)	NR
Wang 2004, p. 2085 (Swerdloff 2003 p.207)	19–68 yr	36 mo	1% gel, 50 mg/d (NR) 1% gel, 75 mg/d (NR) 1% gel, 100 mg/d (NR)	51.5 (0.9)	14.1 (1.3) ¶¶ 22.4 (2.7) 25.6 (2.4)	No

Note: DPE = diet plus exercise, ED = erectile dysfunction, IHH = Idiopathic hypogonadotropic hypogonadism, IM = intramuscular, IQR = interquarile range, LOH = late-onset hypogonadism, MetS = metabolic syndrome, NR = not reported, SE = standard error, SD = standard deviation, T = testosterone, TC = testosterone cypionate, TE = testosterone enanthate, TRT = testosterone replacement therapy, VA = Veterans Affairs.

*All studies involved men that were either described as hypogonadal and met the cut-off for hypogonadism (total T < 12 nmol/L or free T < 225 pmol/L) or reported total or free T below these cut-off points.

†Unless otherwise stated.

‡Full cohort includes patients with testosterone levels in the normal range; data extracted only for patients with total testosterone < 300 ng/dl (10.4 nmol/L).

¶Blend of estosterone propionate, testosterone phenylpropionate, testosterone isocaproate, and testosterone decanoate.

§Data provided separately for 3 databases. Range represents the high and low ages (SD) across the three databases.

**Baseline testosterone level not reported for the never-TRT group. In both the TRT group and the no TRT group, 98%–99% of patients were reported to have total T < 10.4 nmol/L at baseline.

††Mean total testosterone level not provide among patients with a "low" testosterone level (< 10.4 nmol/L).

‡‡Study eligibility was total T < 300 ng/dl or free T < 50 pg/ml.

¶¶Long term extension of an included RCT (Wang 2000). Total testosterone levels reported here are after 6 months of TRT treatment in the RCT.

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eTable 3: Risk of bias of included randomized controlled trials that reported at least one outcome of interest

Author, year	Adequate sequence generation	Allocation concealment	Blinding of outcome assessment (objective outcomes)	Blinding of outcome assessment (subjective outcomes)	Incomplete outcome data addressed (efficacy outcomes)	Incomplete outcome data addressed (harm outcomes)
Dias 2016	Low	Unclear	Low	Low	High	Unclear
Chillarón 2016	Unclear	Low	Low	Unclear	Low	Low
Brock 2016	Low	Low	Low	Low	Low	Low
Dhindsa 2016	Unclear	Unclear	Low	Unclear	High	Unclear
Konaka 2016	Low	Unclear	Low	High	High	Unclear
Magnussen 2016	Low	Low	Low	Low	Low	Low
Ng Tang Fui 2016	Low	Low	Low	Low	High	Unclear
Sinclair 2016	Unclear	Low	Low	Low	High	High
Snyder 2016	Low	Low	Low	Low	Low	Low
Basaria 2015, p. 570	Unclear	Unclear	Low	Low	High	Unclear
Basaria 2015, p. 280	Low	Unclear	Low	Low	High	Unclear
Cherrier 2015	Unclear	Unclear	Low	Unclear	Low	Low
Paduch 2015	Low	Low	Low	Unclear	Low	Low
Gianatti 2014	Unclear	Low	Low	Low	Low	Low
Borst 2014	Low	Unclear	Low	High	High	High
Hackett 2013	Unclear	Low	Low	Low	Low	Low
Wang 2013	Unclear	Unclear	Low	NA	Low	High
Behre 2012	Low	Low	Low	Low	Low	High
Spitzer 2012	Unclear	Low	Low	Low	Low	Low
Stout 2012	Unclear	Unclear	NA	Low	High	High
Zhang 2012	Unclear	Low	Low	High	Low	Low
Ho 2011	Unclear	Low	Low	Low	Low	Low
Jones 2011	Unclear	Unclear	Low	Low	High	High
Kaufman 2011	Unclear	Low	Low	Low	High	Low
Sheffield-Moore 2011	Unclear	Low	Low	NA	Low	High
Shigehara 2011	Unclear	Unclear	Low	High	Low	Low
Aversa 2010, p. 776	Unclear	Unclear	Low	Low	Unclear	Unclear
Aversa 2010, p. 3495	Unclear	Unclear	Low	Low	Low	Low
Basaria 2010	Low	Low	Low	Low	Low	Unclear
Kalinchenko 2010	Unclear	Low	Low	Low	Low	Low
Kenny 2010	Unclear	Low	Low	Low	High	Unclear
Srinivas-Shankar 2010	Low	Low	Low	Low	Low	Unclear
Caminiti 2009	Unclear	Low	Low	Low	Low	Low
Chiang 2009	Unclear	Unclear	Low	Low	High	High

Emmelot-Vonk 2009	Low	Low	Low	Low	Low	Low
Heufelder 2009	Low	Unclear	Low	High	Low	Low
Hohl 2009	High	High	Low	High	Low	Low
Mathur 2009	Low	Unclear	Low	Low	Low	High
Morales 2009	Low	Low	Low	Low	Low	Low
Shores 2009	Low	Low	Low	Low	High	Unclear
Agledahl 2008	Unclear	Unclear	Low	NA	Low	Low
Basurto 2008	Low	Low	Low	Low	Low	Unclear
Raynaud 2008	Unclear	Unclear	Low	High	High	High
Svartberg 2008	Unclear	Unclear	Low	Low	Low	Unclear
Chiang 2007	Unclear	Unclear	Low	Unclear	High	Low
Brockenbrough 2006	Unclear	Low	Low	Unclear	High	Low
Marks 2006	Unclear	Unclear	Low	Low	Low	Low
Merza 2005	Unclear	Unclear	Low	Unclear	Low	Low
Kuhnert 2005	Unclear	Low	Low	High	High	High
Orengo 2005	Low	Unclear	Low	Unclear	High	High
Amory 2004	Low	Low	Low	Low	Unclear	Unclear
Cavallini 2004	Unclear	Unclear	Low	Unclear	Unclear	High
Schubert 2004	Low	Unclear	Low	High	Unclear	Low
Shabsigh 2004	Low	Unclear	Low	Low	Low	Unclear
Boyanov 2003	Unclear	Unclear	Low	High	Low	Low
McNicholas 2003	Unclear	Unclear	Low	High	High	High
Steidle 2003	Unclear	Unclear	Low	High	High	High
Tan 2003	Unclear	Unclear	Unclear	High	Low	Low
Ferrando 2002	Unclear	Unclear	Low	NA	Low	Low
Kang 2002	Unclear	Unclear	Low	NA	Low	Low
Simon 2001	Unclear	Unclear	Low	Low	NA	Low
Bhasin 2000	Low	Unclear	Low	Unclear	Low	Unclear
Wang 2000	Unclear	Unclear	Low	High	High	High
Clague 1999	Unclear	Unclear	Low	NA	Low	Low
Dobs 1999	Unclear	Low	Low	High	High	Unclear
Bhasin 1998	Unclear	Unclear	Low	Unclear	High	Unclear
Grinspoon 1998	Low	Low	Low	Low	High	Unclear
Jockenhovel 1997, p. 2510	Unclear	Unclear	Low	NA	Unclear	Unclear
Jockenhovel 1997, p. 293	Unclear	Unclear	Low	NA	Low	Unclear
Sih 1997	Low	Unclear	Low	Unclear	High	Unclear

Note: Risk of bias was not assessed for the studies that reported no outcomes of interest or that did not provide usable data (e.g., cross-over studies without first period data reported separately).

eTable 4: SIGN50 assessment of included non-randomized studies that reported at least one outcome of interest. Overall assessment was based on consideration of all domains of the SIGN50 Methodology checklist for cohort studies.

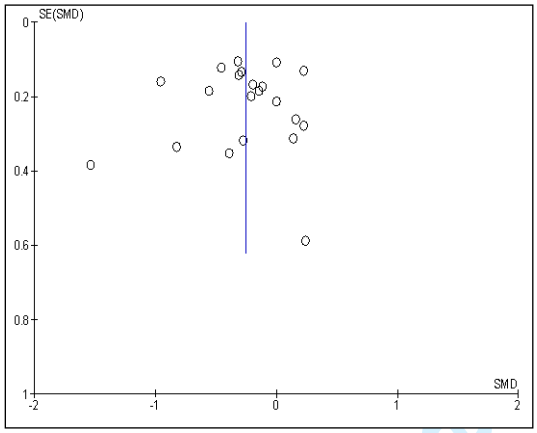
Study*	Overall assessment†	Comments
Traish 2017	Unacceptable (–)	Prospective cohort. Study "not designed or powered to address the effects of [TRT] on mortality in men with hypogonadism." Control group comprised men who opted against TRT. Did not adjust adjust for previous CV events, and groups were not balanced at baseline for some factors. Unclear from where participants were recruited and whether outcome assessment was blinded to exposure status. Outcomes assessed for up to 8 years.
Jung 2016	Unacceptable (–)	Prospective cohort. Did not report how study participants were assigned to treatment groups. Unblinded, with 8 month treatment and follow-up
Debruyne 2017	Acceptable (+)	Prospective cohort. Multinational registry of treated or untreated newly diagnosed hypogonadal men.Follow-up on 93% of cohort over 3-yr period. Included a wide age range and multiple comorbiditie but goups not well balanced across all baseline characteristics. Men with a history of prostate cancer were excluded. Outcome assessment blinded to exposure status.
Layton 2015	Acceptable (+)	Retrospective cohort. Comparative safety of TRT products grouped by route of administration (no comparison to non-users). Data unavailable for some patient characteristics. Study included a "large diverse patient sample representing men across age groups, populations, treatment and practice patterns, and health care systems." Unclear whether outcome assessment was blinded to exposure status. Mean treatment duration between 96 and 122 days.
Cheetham 2017	Acceptable (+)	Retrospective cohort. Cohort entry determind by dispensation of a TRT product. Over 50% of cohort prescribed an intramuscular TRT. Possible confounding by indication, analysis could not adust for all CV risk factors, and dose and duration of TRT were not considered. Unclear whether outcome assessment was blinded to exposure status. Length of follow up about 1 year longer for no TRT group.
Yassin 2017	Unacceptable (–)	Prospective registry. Investigation and biopsy frequency equal in both groups. Outcome assessment not blinded to exposure status. Percentage of cohort for whom data were available not reported. Confounding not considered.
Pastuszak 2015	Unacceptable (–)	Retrospective cohort. Considerable variation in baseline characteristics between groups, and confounding not considered. Outcome assessment not blinded to exposure status. 36 month follow-up.
Ramasay 2015	Unacceptable (–)	Retrospective cohort. "All major adverse cardiovascular events were verified by telephone with the patient (or family members if patient died)." Authors did not provide clear description and measurement about the outcomes. Median follow-up 3.8 (TRT) or 3.4 (no TRT) yr. Confounding not considered, and outcome assessment not blinded to exposure status.
Francomano 2014	Unacceptable (–)	Prospective cohort. Obese men with low testosterone. Baseline characteristics were well matched on reported characteristics, but control group had contraindications to TRT. 33% dropout in treatment group, zero in control group; no comparison between those who dropped out or remained in study.

Aydogdu 2013	Acceptable (+)	Retrospective cohort. Men with IHH. SAE not defined as an outcome but reported that no SAEs were detected for any treatment group.
Blick 2013	Acceptable (+)	Prospective cohort. Groups were generally well matched on baseline characteristics with no statistically significant differences (except for study site). Patients in the 2 treatment groups were not followed for an equal length of time (Androgel: mean 6.1 yr; Testim: mean 1.9 yr). Skin reactions assessed but not reported. Outcome assessment was not blinded to exposure status.
Vigen 2013	Acceptable (+)	Retrospective cohort. All-cause mortality assessed via the Veterans Affairs vital status file. Myocardial infarction and ischemic stroke assessed via ICD-9 codes from Veterans Affairs inpatient treatment files. Conclusions based on a composite outcome. Sufficient data not reported to allow analysis of stroke or MI separately at each time point. Outcome assessment not blinded to exposure status.
Aversa 2012	Unacceptable (–)	Prospective cohort. Men with multiple sclerosis and late onset hypogonadism. Baseline characteristics were well matched; however, control group was comprised of men who had refused or had contraindications to testosterone. Adherence to treatment over 3 years was 50% in TU group.
Shores 2012	Acceptable (+)	Retrospective cohort. Hazard ratio for mortality took person-years of observation into account. Adjusted HR and CIs provided. Outcome assessment not blinded to exposure status. Exposure determined via Veterans Affairs pharmacy records and outcomes ascertained from 2 mortality databases.
Rhoden 2006	Acceptable (+)	Retrospective cohort. Patients had to have negative prostate biopsy before initiation of TRT, thus excluding any men with pre-existing large volume disease. Type and dose of IM testosterone not reported. Dose of gel not reported (data NR by type). Outcome assessment not blinded to exposure status.
Dean 2005	Unacceptable (–)	Prospective cohort. Poor reporting of the number of patients in each group and which group the safety events occurred in. Number of and reasons for withdrawals not reported. Safety data reported overall but not by treatment group. Outcome assessment not blinded to exposure status.
Wang 2004	Unacceptable (–)	Prospective cohort (open-label extension of an RCT). The number of men assigned to each group NR. Safety data poorly reported: 3 cases of prostate cancer reported but number of people in each group not reported. Outcome assessment not blinded to exposure status.
Guay 2000	Unacceptable (–)	Retrospective cohort. Safety data not reported by treatment group. Outcome assessment not blinded to exposure status.
Hajjar 1997	Unacceptable (–)	Retrospective cohort. Data not clearly provided. Safety outcomes were reported based on a subset of people assigned to each group, and it is not clear why the other patients were omitted. Outcome assessment not blinded to exposure status.

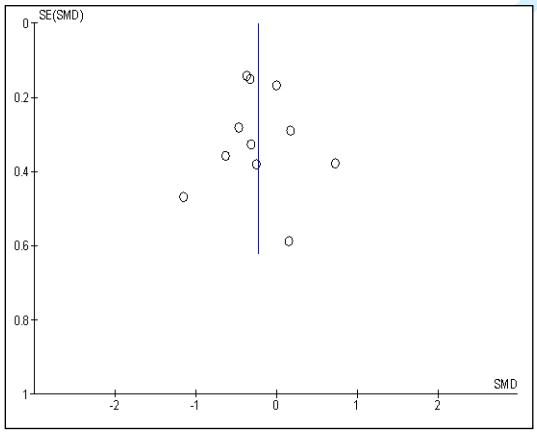
Note: CI = confidence interval, ICD-9 = International Classification of Diseases, Ninth Revision, IHH = idiopathic hypogonadotropic hypogonadism, HR = hazard ratio, MI = myocardial infarction, NR = not reported, RCT = randomized controlled trial, SAE = serious adverse events, TRT = testosterone replacement therapy, TU = testosterone undecanoate.
*Non-randomized studies that reported at least 1 outcome of interest.
†Assessed by use of SIGN50 for cohort studies (www.sign.ac.uk/checklists-and-notes.html).

eAppendix 5: Funnel plots for assessment of publication bias

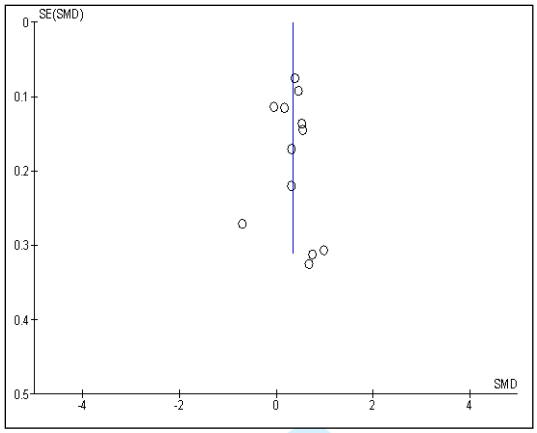
A) Quality of life



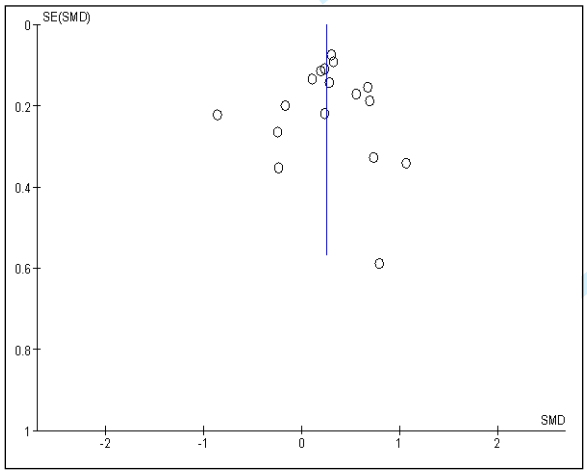
B) Depression



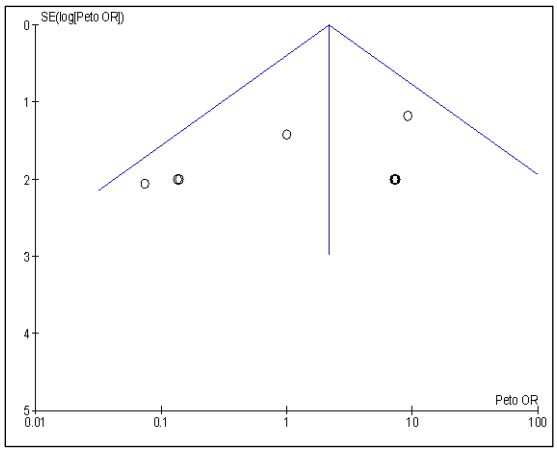
C) Libido



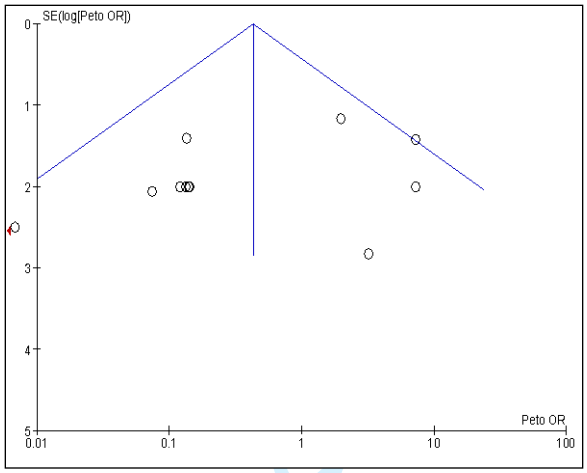
D) Erectile function



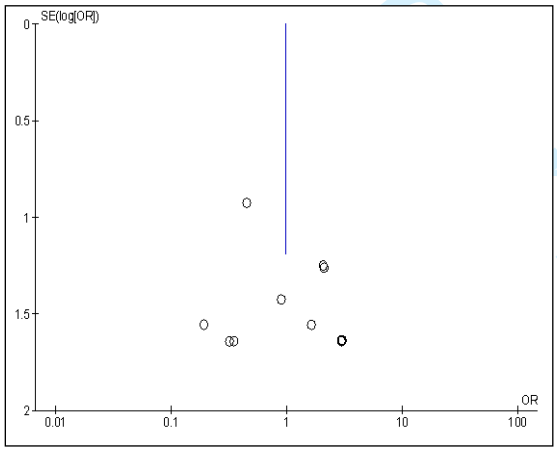
E) Cardiovascular death



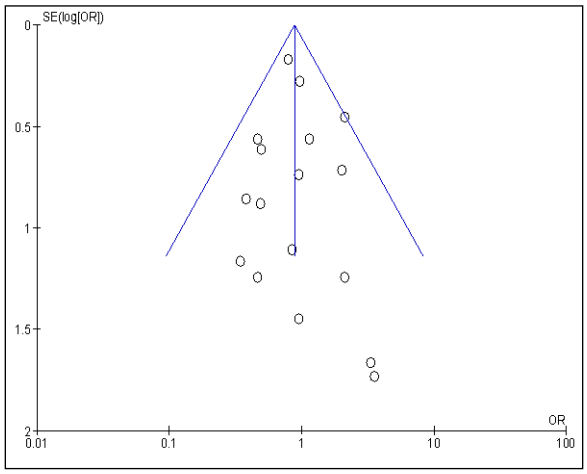
F) Myocardial infarction



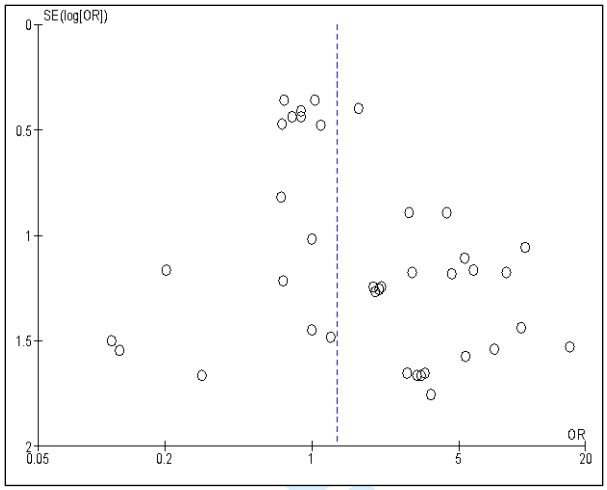
G) Prostate cancer



H) Serious adverse events



I) Withdrawals due to adverse events



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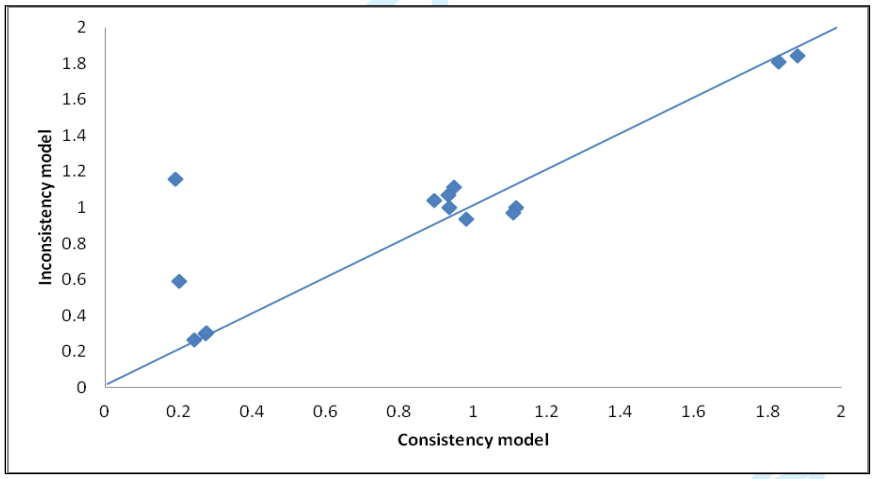
eAppendix 6: Evaluation of network consistency

We evaluated the consistency of networks with closed loops. To be classified as a "closed loop," at least 2 nodes had to be connected by more than one trial (e.g., not connected solely by a multi-arm trial).

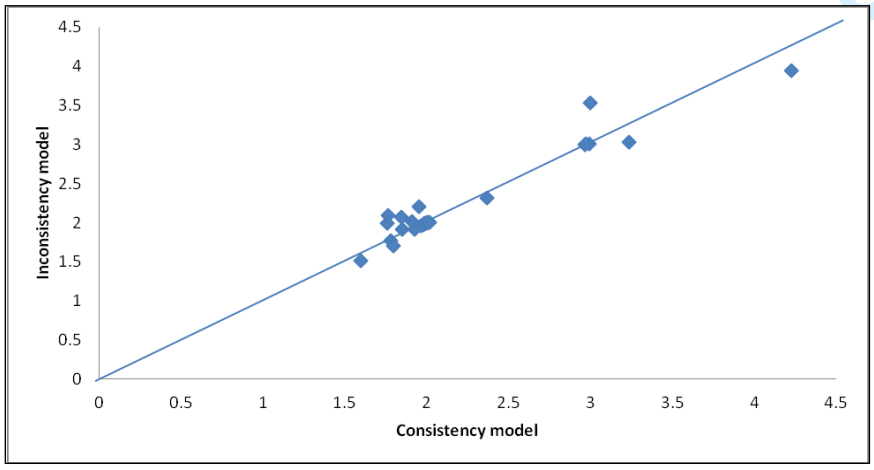
To evaluate the consistency of networks with closed loops, two analyses were performed. One was conducted using the standard consistency model, which assumes that the data in the network are consistent. A second analysis was performed using an inconsistency model, which assumes that the data in the network are not consistent. The posterior mean deviance of the individual data points derived from the inconsistency model was plotted against the posterior mean deviance derived from the consistency model. If inconsistency is present, data points will lie under the diagonal line, indicating deviation from the consistency model. Data points above the diagonal line indicate deviation from the inconsistency model and are not indicative of inconsistency.

Model fit was also evaluated by considering the residual deviance and deviance information criterion (DIC) of the inconsistency and consistency models, with the model that has the lower residual deviance and DIC representing the better fit for the data. For each network, the consistency model had a lower residual deviance and DIC for each outcome, representing better model fit.

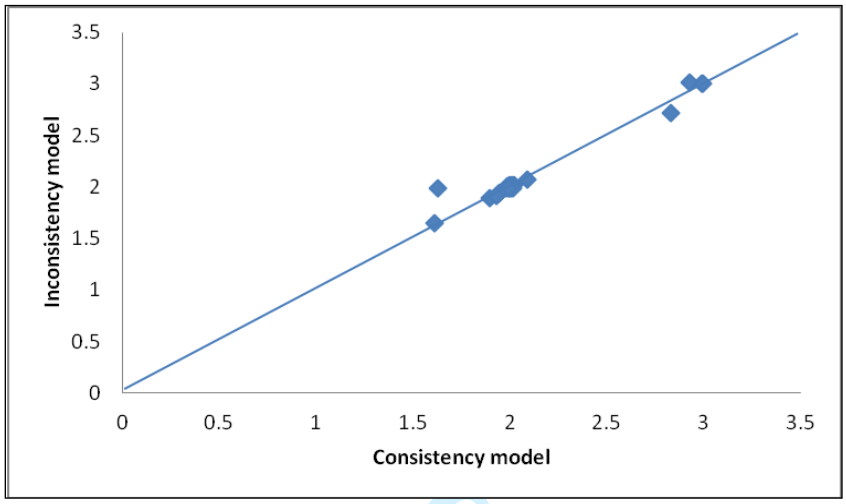
LIBIDO: BASE CASE (ALL STUDIES)



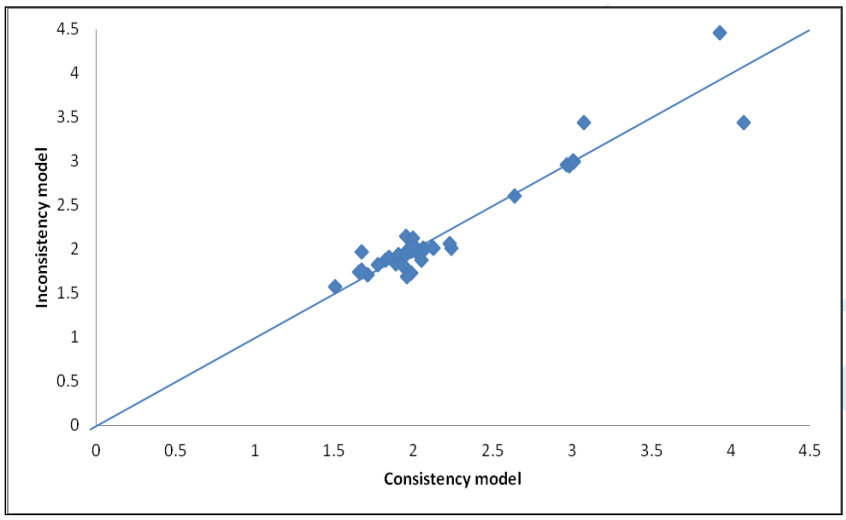
TOTAL TESTOSTERONE LEVEL, 3 MO



TOTAL TESTOSTERONE LEVEL, 6 MO



TOTAL TESTOSTERONE LEVEL, END OF STUDY



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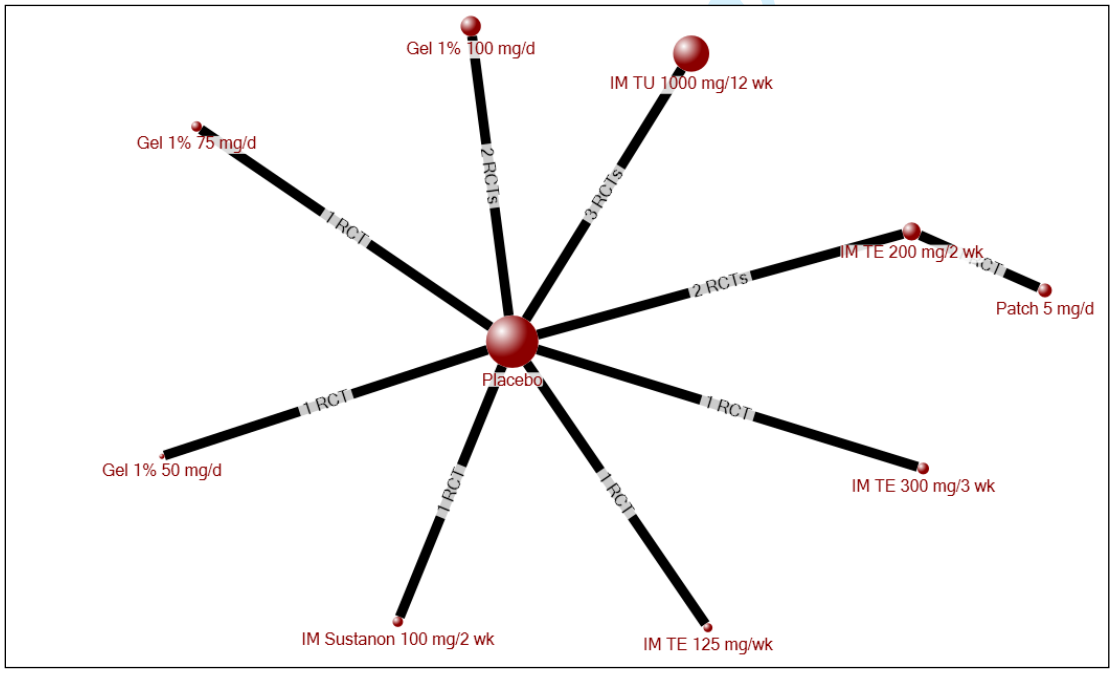
eAppendix 7: Evidence networks

Summary of network characteristics

Outcome	No. of trials	No. of treatments*	No. of comparisons†	No. of participants	Treatment duration
Quality of life	23	14	27	3090	12 wk to 3 yr
Depression	12	9	12	852	12 wk to 3 yr
Libido	14	10	23	3167	12 wk to 3 yr
Erectile function	17	9	19	3165	12 wk to 3 yr
Total testosterone, 3 mo	26	15	39	2739	NA
Total testosterone, 6 mo	23	18	29	2908	NA
Total testosterone, end of study	57	28	74	5538	12 wk to 3 yr
Serious AEs	15	7	15	1860	12 to 3 yr
Withdrawals due to AEs	27	16	29	4165	12 wk to 3 yr

Note: AE = adverse event.
*In addition to placebo
†Direct comparisons based on the number of 2-, 3-, and 4-arm trials.

eFigure 1A) Depression



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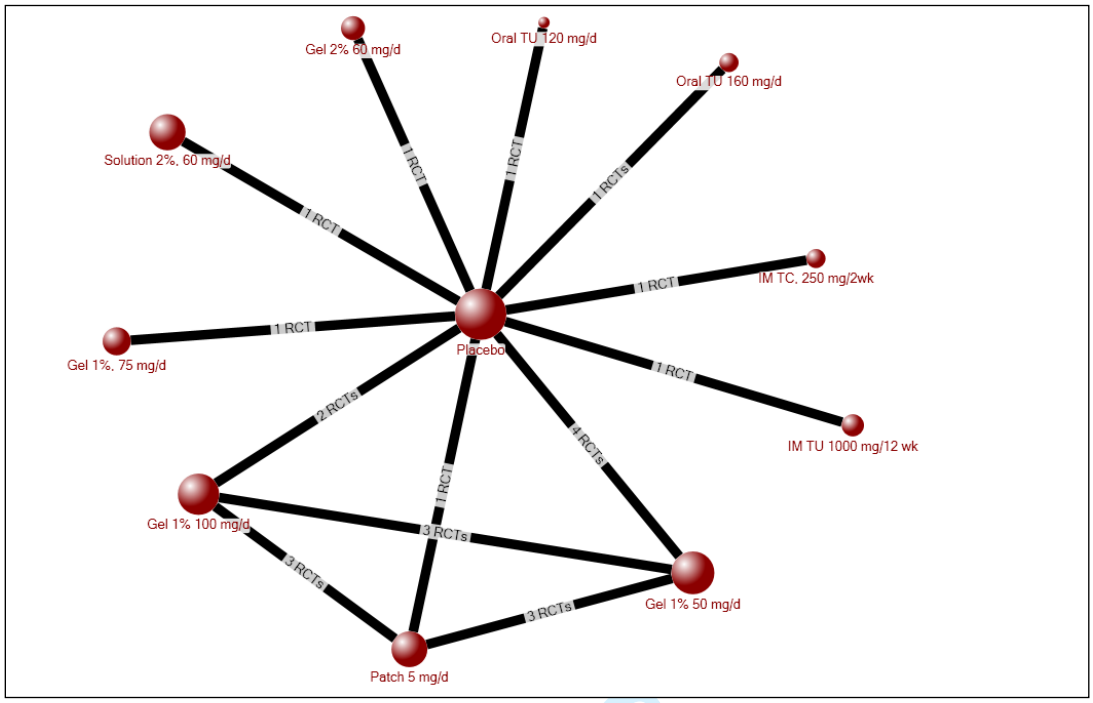
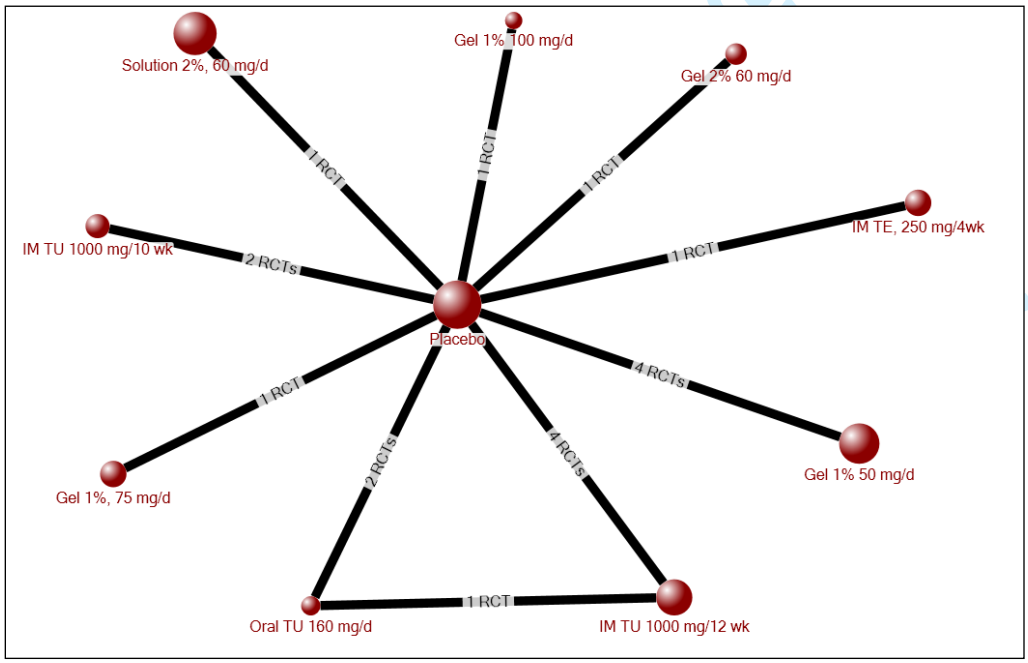
B) Libido



C) Erectile function



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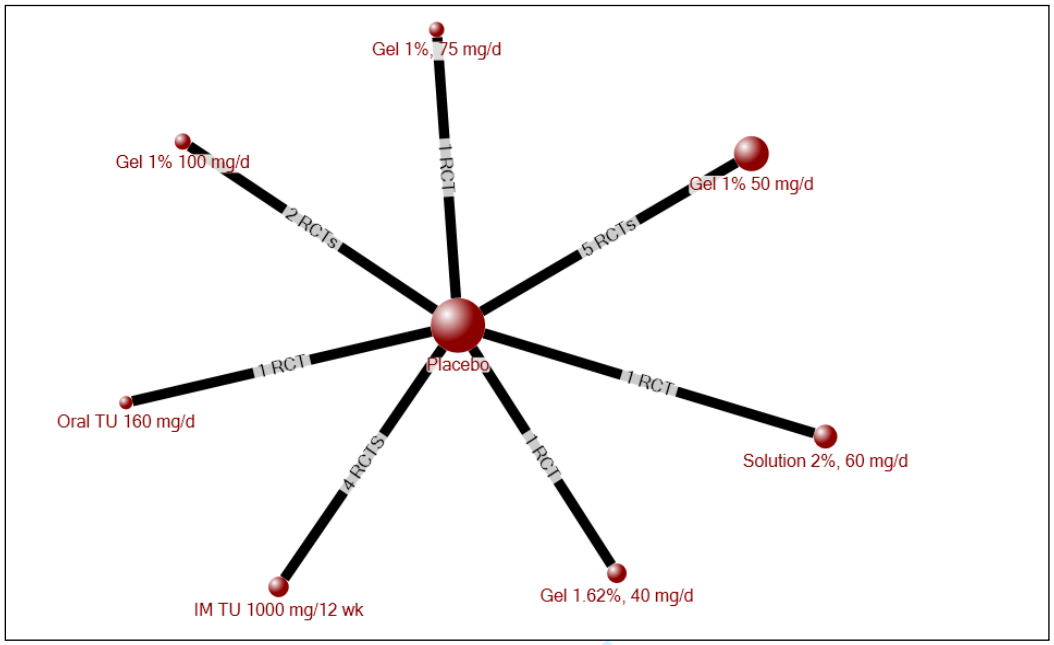
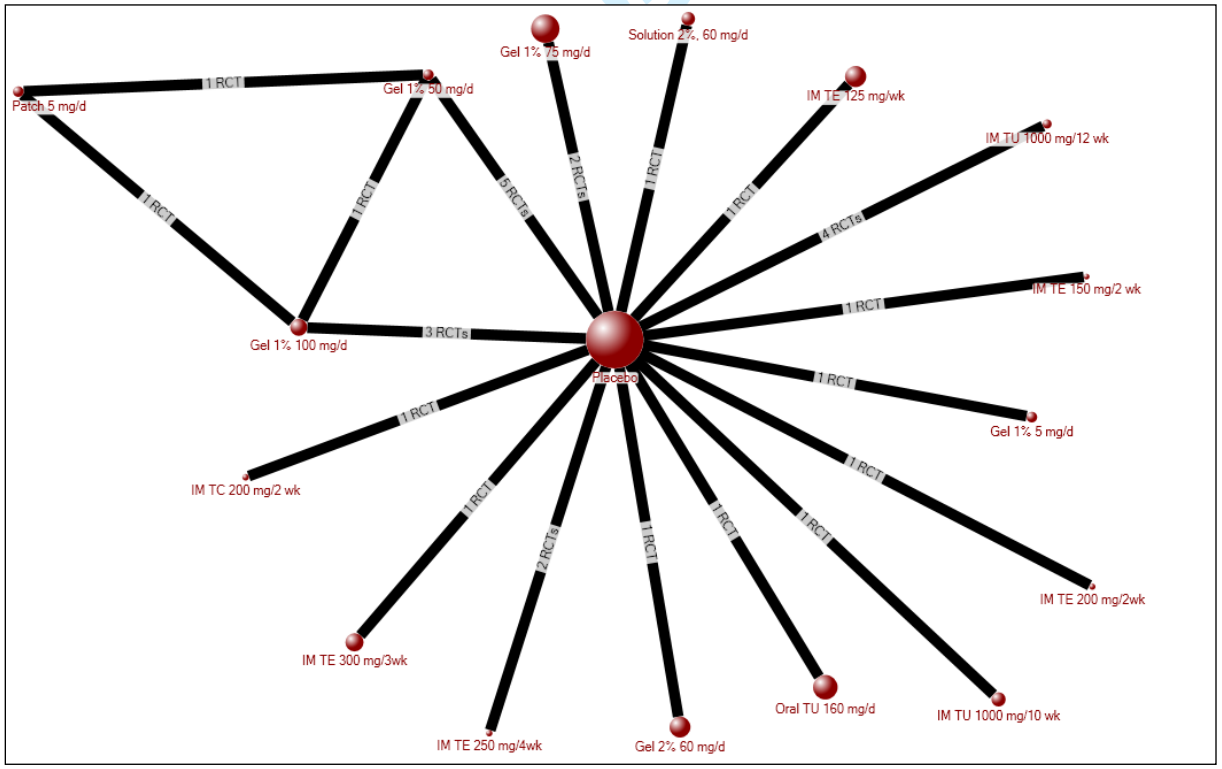
D) Serious adverse events



E) Withdrawals due to adverse events



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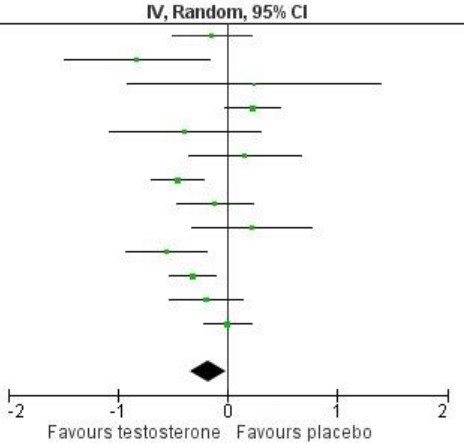
eAppendix 8: Pair-wise meta-analyses and network meta-analyses

eFigure 2: Individual trial results, quality of life, among men without major comorbidities

Study or Subgroup	Testosterone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Basaria 2015, p. 580	2	15.1	60	3.9	10.5	58	8.4%	-0.14 [-0.51, 0.22]	
Merza 2005	-0.4	13.3	20	10.6	12.8	19	4.3%	-0.83 [-1.48, -0.17]	2005
Orengo 2005	-3	4.5	7	-4.6	8	5	1.7%	0.24 [-0.91, 1.39]	2005
Emmelot-Vonk 2009	5	18	120	0.6	20.8	117	10.5%	0.23 [-0.03, 0.48]	2009
Shores 2009	-1.8	6.8	17	1.3	8.6	16	4.0%	-0.39 [-1.08, 0.30]	2009
Morales 2009	-3.4	8.3	29	-4.6	6.6	29	5.8%	0.16 [-0.36, 0.67]	2009
Srinivas-Shankar 2010	-2.8	2.8	138	-1.5	2.9	136	10.9%	-0.45 [-0.69, -0.21]	2010
Kenny 2010	-0.2	0.8	69	-0.1	0.9	62	8.7%	-0.12 [-0.46, 0.23]	2010
Shigehara 2011	0.3	6.2	26	-1	5.2	26	5.5%	0.22 [-0.32, 0.77]	2011
Ho 2011	-9.1	7.7	60	-4.9	7.2	60	8.3%	-0.56 [-0.92, -0.19]	2011
Behre 2012	-10.5	10.1	183	-7.2	10.4	179	11.6%	-0.32 [-0.53, -0.11]	2012
Spitzer 2012	-10	18.9	70	-6	21.8	70	8.9%	-0.19 [-0.53, 0.14]	2012
Konaka 2016	-1	7.6	169	-1	7.7	165	11.4%	0.00 [-0.21, 0.21]	2016
Total (95% CI)			**968**			**942**	**100.0%**	**-0.17 [-0.34, -0.01]**	

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 31.86$, df = 12 (P = 0.001); $I^2 = 62\%$

Test for overall effect: Z = 2.10 (P = 0.04)



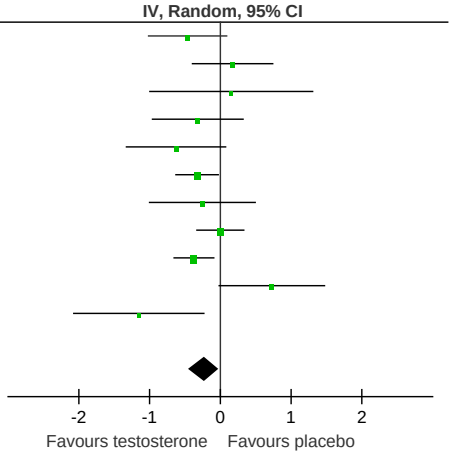
eFigure 3: Individual trial results, depression

A) All trials

Study or Subgroup	Testosterone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Grinspoon 1998	-5.8	6.6	26	-2.7	6.6	26	9.2%	-0.46 [-1.01, 0.09]	1998
Amory 2004	-0.2	0.4	24	-0.3	0.7	24	8.9%	0.17 [-0.39, 0.74]	2004
Orengo 2005	-6	2.6	7	-6.8	6.9	5	3.0%	0.15 [-1.00, 1.30]	2005
Svartberg 2008	-1.3	2.9	19	-0.5	1.9	19	7.6%	-0.32 [-0.96, 0.32]	2008
Shores 2009	-4.3	3.1	17	-2.4	2.8	16	6.6%	-0.63 [-1.33, 0.07]	2009
Kalinchenko 2010	-3.6	5.3	113	-1.9	4.9	71	16.2%	-0.33 [-0.63, -0.03]	2010
Stout 2012	-3.8	6.1	15	-2.5	3.2	13	6.1%	-0.25 [-1.00, 0.49]	2012
Spitzer 2012	2	11.5	70	2	11.5	70	15.1%	0.00 [-0.33, 0.33]	2012
Hackett 2013	-1.1	3.9	97	0.4	4.1	102	16.9%	-0.37 [-0.65, -0.09]	2013
Borst 2014	1	2.2	14	-0.3	1.2	16	6.1%	0.73 [-0.02, 1.47]	2014
Cherrier 2015	-2.8	4.7	10	2.7	4.5	12	4.4%	-1.15 [-2.07, -0.23]	2015
Total (95% CI)			**412**			**374**	**100.0%**	**-0.23 [-0.44, -0.01]**	

Heterogeneity: Tau² = 0.05; Chi² = 17.84, df = 10 (P = 0.06); I² = 44%

Test for overall effect: Z = 2.08 (P = 0.04)

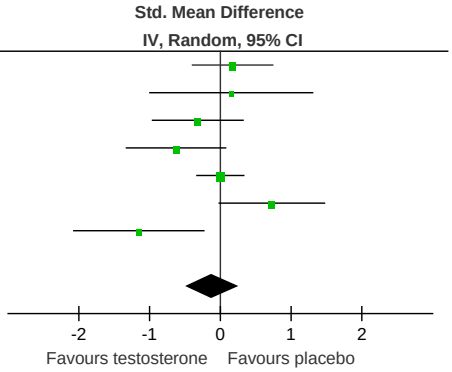


B) Trials involving men without major comorbidities

Study or Subgroup	Testosterone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Amory 2004	-0.2	0.4	24	-0.3	0.7	24	16.9%	0.17 [-0.39, 0.74]	2004
Orengo 2005	-6	2.6	7	-6.8	6.9	5	7.7%	0.15 [-1.00, 1.30]	2005
Svartberg 2008	-1.3	2.9	19	-0.5	1.9	19	15.3%	-0.32 [-0.96, 0.32]	2008
Shores 2009	-4.3	3.1	17	-2.4	2.8	16	14.0%	-0.63 [-1.33, 0.07]	2009
Spitzer 2012	2	11.5	70	2	11.5	70	22.6%	0.00 [-0.33, 0.33]	2012
Borst 2014	1	2.2	14	-0.3	1.2	16	13.2%	0.73 [-0.02, 1.47]	2014
Cherrier 2015	-2.8	4.7	10	2.7	4.5	12	10.4%	-1.15 [-2.07, -0.23]	2015
Total (95% CI)			**161**			**162**	**100.0%**	**-0.12 [-0.49, 0.26]**	

Heterogeneity: Tau² = 0.13; Chi² = 13.76, df = 6 (P = 0.03); I² = 56%

Test for overall effect: Z = 0.62 (P = 0.53)



eTable 5: Depression – Bayesian network meta-analysis*

Treatment	Standardized mean difference (95% confidence interval)									
	Placebo	Patch, 5 mg/d	Gel 1%, 50 mg/d	Gel 1%, 75 mg/d	Gel 1%, 100 mg/d	IM TU, 1000 mg/12 wk	IM TE, 125 mg/ wk	IM TE, 200 mg/ 3 wk	IM TE, 300 mg/ 3 wk	IM Sustanon, 100 mg/ 2 wk
Patch, 5 mg/d	-0.10 (-2.43,2.32)	—								
Gel 1%, 50 mg/d	0.17 (-1.72,2.00)	0.27 (-2.76,3.22)	—							
Gel 1%, 75 mg/d	-0.63 (-2.35,1.10)	-0.54 (-3.46,2.37)	-0.80 (-3.33,1.74)	—						
Gel 1%, 100 mg/d	-0.38 (-1.71,0.65)	-0.28 (-3.12,2.20)	-0.55 (-2.87,1.55)	0.25 (-2.00,2.18)	—					
IM TU, 1000 mg/12 wk	-0.34 (-1.29,0.61)	-0.24 (-2.82,2.31)	-0.51 (-2.55,1.59)	0.29 (-1.67,2.22)	0.04 (-1.32,1.72)	—				
IM TE 125 mg/wk	0.69 (-1.02,2.42)	0.79 (-2.12,3.67)	0.52 (-1.97,3.10)	1.32 (-1.12,3.76)	1.07 (-0.87,3.31)	1.03 (-0.94,3.00)	—			
IM TE, 200 mg/2 wk	0.18 (-1.47,1.91)	0.28 (-1.38,1.92)	0.01 (-2.42,2.56)	0.82 (-1.58,3.20)	0.56 (-1.32,2.81)	0.53 (-1.38,2.51)	-0.51 (-2.88,1.91)	—		
IM TE, 300 mg/3 wk	-0.46 (-2.13,1.22)	-0.36 (-3.26,2.50)	-0.63 (-3.10,1.89)	0.17 (-2.22,2.53)	-0.08 (-1.95,2.12)	-0.12 (-2.05,1.81)	-1.15 (-3.54,1.29)	-0.64 (-3.02,1.67)	—	
IM Sustanon, 100 mg/2 wk†	-0.25 (-1.98,1.43)	-0.15 (-3.09,2.72)	-0.42 (-2.93,2.11)	0.38 (-2.11,2.79)	0.13 (-1.84,2.33)	0.09 (-1.92,2.06)	-0.94 (-3.39,1.45)	-0.44 (-2.87,1.92)	0.21 (-2.23,2.58)	—

Note: IM = intramuscular, TE = testosterone enanthate, TU = testosterone undecanoate.
*Random effects model. Analysis based on change from baseline. A negative SMD indicates improvement in depression. Significant changes are indicated by use of bold and colour (green indicates that the row treatment is significantly better than the column treatment, while red indicates that the row treatment is significantly worse than the column treatment). White indicates no significant difference between treatments.
†Blend of testosterone propionate, testosterone phenylpropionate, testosterone isocaproate, and testosterone decanoate.

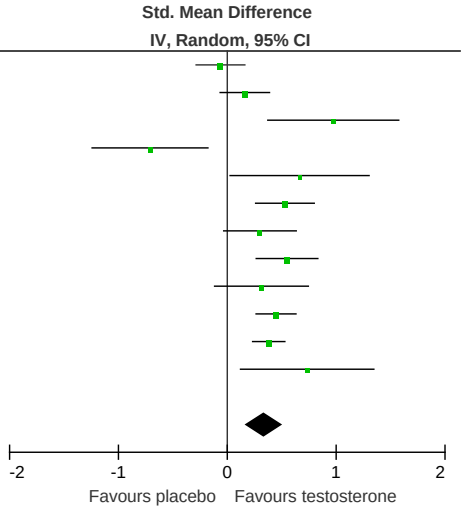
eFigure 4: Individual trial results, libido

A) All trials

Study or Subgroup	Testosterone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Basaria 2015, p. 580	0.1	1.5	156	0.2	1.7	152	10.7%	-0.06 [-0.29, 0.16]	
Steidle 2003	0.7	1.3	307	0.5	1	99	10.6%	0.16 [-0.07, 0.39]	2003
Boyanov 2003	0.9	0.6	24	0.2	0.8	24	5.0%	0.97 [0.37, 1.57]	2003
Morales 2009	0.1	1.2	29	1	1.3	29	5.7%	-0.71 [-1.24, -0.18]	2009
Chiang 2009	1.4	1.8	20	0	2.3	20	4.6%	0.66 [0.03, 1.30]	2009
Jones 2011	1	1.4	108	0.2	1.6	112	9.9%	0.53 [0.26, 0.80]	2011
Spitzer 2012	0.7	2.6	70	0	2	70	8.7%	0.30 [-0.03, 0.63]	2012
Hackett 2013	0.5	1.4	97	-0.3	1.5	102	9.6%	0.55 [0.27, 0.83]	2013
Basaria 2015, p. 280	1.1	3.6	43	0.1	2.6	41	7.1%	0.31 [-0.12, 0.74]	2015
Snyder 2016	2.6	6.5	234	0	5	236	11.4%	0.45 [0.26, 0.63]	2016
Brock 2016	1.2	2.1	358	0.4	2.1	357	11.9%	0.38 [0.23, 0.53]	2016
Dhindsa 2016	1.2	1.1	22	0.3	1.3	22	4.8%	0.73 [0.12, 1.35]	2016
Total (95% CI)			**1468**			**1264**	**100.0%**	**0.33 [0.16, 0.50]**	

Heterogeneity: Tau² = 0.06; Chi² = 42.25, df = 11 (P < 0.0001); I² = 74%

Test for overall effect: Z = 3.85 (P = 0.0001)

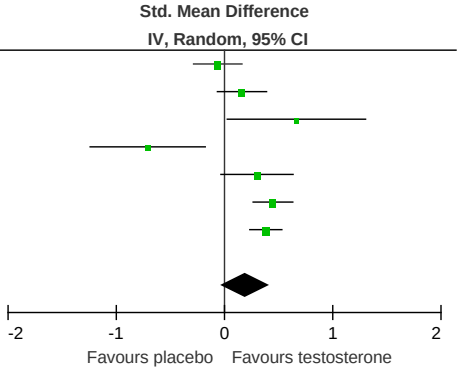


B) Trials involving men with no major comorbidities

Study or Subgroup	Testosterone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Basaria 2015, p. 580	0.1	1.5	156	0.2	1.7	152	16.7%	-0.06 [-0.29, 0.16]	
Steidle 2003	0.7	1.3	307	0.5	1	99	16.6%	0.16 [-0.07, 0.39]	2003
Chiang 2009	1.4	1.8	20	0	2.3	20	7.4%	0.66 [0.03, 1.30]	2009
Morales 2009	0.1	1.2	29	1	1.3	29	9.2%	-0.71 [-1.24, -0.18]	2009
Spitzer 2012	0.7	2.6	70	0	2	70	13.8%	0.30 [-0.03, 0.63]	2012
Snyder 2016	2.6	6.5	234	0	5	236	17.7%	0.45 [0.26, 0.63]	2016
Brock 2016	1.2	2.1	358	0.4	2.08	357	18.5%	0.38 [0.23, 0.53]	2016
Total (95% CI)			**1174**			**963**	**100.0%**	**0.19 [-0.03, 0.41]**	

Heterogeneity: Tau² = 0.06; Chi² = 29.74, df = 6 (P < 0.0001); I² = 80%

Test for overall effect: Z = 1.72 (P = 0.09)



eTable6: Libido – Bayesian network meta-analysis*

	Standardized mean difference (95% confidence interval)										
	Placebo	Patch, 5 mg/d	Gel 1%, 50 mg/d	Gel 1%, 75 mg/d	Gel 1%, 100 mg/d	Gel 2%, 60 mg/d	Solution 2%, 60 mg/d	Oral TU, 120 mg/d	Oral, TU 160 mg/d	IM TU, 1000 mg/ 12 wk	IM TC, 250 mg/2wk
Patch, 5 mg/d	0.17 (-0.13,0.46)	—									
Gel 1%, 50 mg/d	**0.32 (0.10,0.55)**	0.15 (-0.10,0.42)	—								
Gel 1%, 75 mg/d	-0.06 (-0.49,0.36)	-0.23 (-0.75,0.29)	-0.38 (-0.87,0.10)	—							
Gel 1%, 100 mg/d	**0.43 (0.16,0.69)**	**0.26 (0.00,0.52)**	0.11 (-0.14,0.35)	0.49 (-0.01,0.99)	—						
Gel 2%, 60 mg/d	**0.54 (0.09,0.99)**	0.37 (-0.17,0.91)	0.21 (-0.29,0.72)	0.60 (-0.01,1.22)	0.11 (-0.41,0.63)	—					
Solution 2%, 60 mg/d	0.39 (-0.01,0.79)	0.22 (-0.28,0.72)	0.07 (-0.39,0.53)	0.45 (-0.12,1.04)	-0.04 (-0.52,0.44)	-0.15 (-0.75,0.46)	—				
Oral TU, 120 mg/d	**1.00 (0.31,1.68)**	**0.83 (0.08,1.58)**	0.68 (-0.05,1.39)	**1.06 (0.25,1.87)**	0.57 (-0.17,1.30)	0.46 (-0.36,1.28)	0.61 (-0.18,1.39)	—			
Oral TU, 160 mg/d	**-0.72 (-1.35,-0.10)**	**-0.89 (-1.58,-0.19)**	**-1.04 (-1.70,-0.38)**	-0.66 (-1.41,0.10)	**-1.15 (-1.83,0.47)**	**-1.26 (-2.01,-0.49)**	**-1.11 (-1.84,-0.37)**	**-1.72 (-2.66,-0.78)**	—		
IM TU, 1000 mg/12 wk	**0.57 (0.11,1.03)**	0.40 (-0.14,0.95)	0.25 (-0.26,0.76)	**0.63 (0.00,1.26)**	0.14 (-0.38,0.67)	0.03 (-0.61,0.68)	0.18 (-0.42,0.79)	-0.43 (-1.25,0.41)	**1.29 (0.52,2.07)**	—	

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IM TC, 250 mg/2wk	**0.71 (0.01,1.41)**	0.55 (-0.21,1.30)	0.39 (-0.34,1.12)	0.78 (-0.05,1.59)	0.29 (-0.46,1.04)	0.18 (-0.65,0.99)	0.33 (-0.47,1.13)	-0.28 (-1.25,0.72)	**1.44 (0.49,2.37)**	0.14 (-0.70,0.97)	—

Note: IM = intramuscular injection, TC = testostereon cypionate, TU = testosterone undecanoate.
*Random effects model. Analysis based on change from baseline. A positive SMD indicates improvement in libido. Significant changes are indicated by use of bold and colour (green indicates that the row treatment is significantly better than the column treatment, while red indicates that the row treatment is significantly worse than the column treatment). White indicates no significant difference between treatments.

Supplemental Online Content: Elliott et al. Testosterone therapy in hypogonadal men: a systematic review and network meta-analysis.

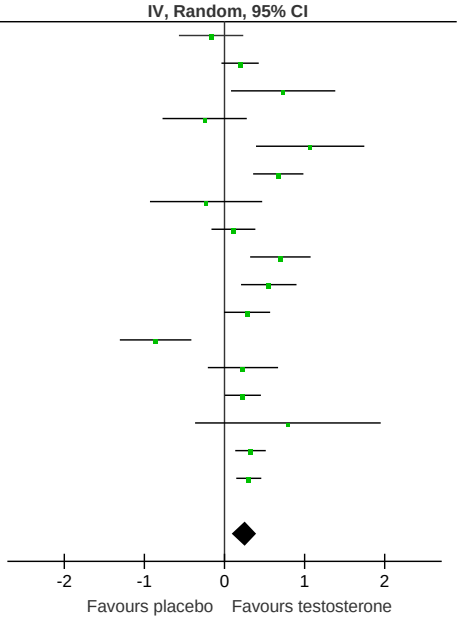
eFigure 5: Individual trial results, erectile function

A) All trials

Study or Subgroup	Testosterone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Ng Tang Fui 2016	0	4.1	49	0.7	4.2	51	5.9%	-0.17 [-0.56, 0.23]	
Basaria 2015, p. 580	1.2	7.7	156	-0.4	8.7	152	7.8%	0.19 [-0.03, 0.42]	
Chiang 2007	5.8	5.8	20	1.2	6.5	20	3.6%	0.73 [0.09, 1.37]	2007
Morales 2009	-0.4	4.7	29	0.9	5.6	29	4.6%	-0.25 [-0.76, 0.27]	2009
Chiang 2009	7.3	7.8	20	-1.6	8.5	20	3.4%	1.07 [0.40, 1.74]	2009
Kalinchenko 2010	3.5	4.6	113	0.4	4.6	71	6.9%	0.67 [0.37, 0.98]	2010
Aversa 2010 p. 776	2.5	2	42	3	2.7	10	3.3%	-0.23 [-0.92, 0.46]	2010
Jones 2011	3.2	6	108	2.5	6.5	112	7.4%	0.11 [-0.15, 0.38]	2011
Ho 2011	2.3	4.8	60	-1	4.6	60	6.1%	0.70 [0.33, 1.07]	2011
Spitzer 2012	2	5.4	70	-1	5.4	70	6.5%	0.55 [0.21, 0.89]	2012
Hackett 2013	0.75	6.6	97	-1.1	6.5	102	7.2%	0.28 [0.00, 0.56]	2013
Gianatti 2014	-2	3.7	45	2	5.4	43	5.4%	-0.86 [-1.30, -0.42]	2014
Basaria 2015, p. 280	2.7	0.9	43	2.4	1.6	41	5.5%	0.23 [-0.20, 0.66]	2015
Konaka 2016	0.2	5.2	169	-1	5.2	165	7.9%	0.23 [0.02, 0.45]	2016
Chillaron 2016	5	7.5	6	0.5	2.1	7	1.5%	0.79 [-0.36, 1.94]	2016
Snyder 2016	3.1	6.9	234	1	6	236	8.3%	0.32 [0.14, 0.51]	2016
Brock 2016	3.4	8.89	358	0.7	8.88	357	8.6%	0.30 [0.16, 0.45]	2016
Total (95% CI)			**1619**			**1546**	**100.0%**	**0.25 [0.10, 0.41]**	

Heterogeneity: Tau² = 0.07; Chi² = 61.56, df = 16 (P < 0.00001); I² = 74%

Test for overall effect: Z = 3.19 (P = 0.001)

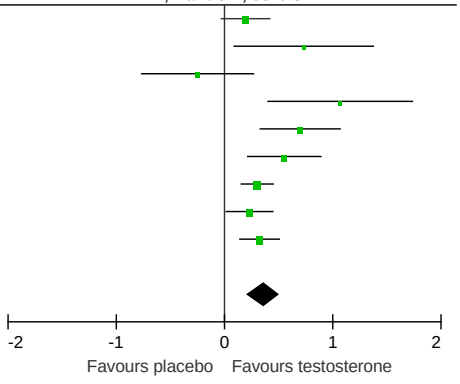


B) Trials involving men without major comorbidities

Study or Subgroup	Testosterone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Basaria 2015, p. 580	1.2	7.7	156	-0.4	8.7	152	15.0%	0.19 [-0.03, 0.42]	
Chiang 2007	5.8	5.8	20	1.2	6.5	20	4.3%	0.73 [0.09, 1.37]	2007
Morales 2009	-0.4	4.7	29	0.9	5.6	29	6.0%	-0.25 [-0.76, 0.27]	2009
Chiang 2009	7.3	7.8	20	-1.6	8.5	20	4.0%	1.07 [0.40, 1.74]	2009
Ho 2011	2.3	4.8	60	-1	4.57	60	9.4%	0.70 [0.33, 1.07]	2011
Spitzer 2012	2	5.4	70	-1	5.4	70	10.4%	0.55 [0.21, 0.89]	2012
Brock 2016	3.4	8.9	358	0.7	8.9	357	18.6%	0.30 [0.16, 0.45]	2016
Konaka 2016	0.2	5.15	169	-1	5.2	165	15.4%	0.23 [0.02, 0.45]	2016
Snyder 2016	3.1	6.9	234	1	6	236	16.9%	0.32 [0.14, 0.51]	2016
Total (95% CI)			**1116**			**1109**	**100.0%**	**0.36 [0.21, 0.51]**	

Heterogeneity: Tau² = 0.02; Chi² = 18.87, df = 8 (P = 0.02); I² = 58%

Test for overall effect: Z = 4.76 (P < 0.00001)



eTable7: Erectile function at end of treatment – Bayesian network meta-analysis*

	Standardized mean difference (95% confidence interval)									
	Placebo	Gel 1%, 50 mg/d	Gel 1%, 75 mg/d	Gel 1%, 100 mg/d	Gel 2%, 60 mg/d	Solution 2%, 60 mg/d	Oral, TU 160 mg/d	IM TU, 1000 mg/10 wk	IM TU, 1000 mg/12 wk	IM TE 250 mg/4wk
Gel 1%, 50 mg/d	0.65 (-0.11,1.42)	—								
Gel 1%, 75 mg/d	0.26 (-0.60,1.11)	-0.39 (-1.55,0.76)	—							
Gel 1%, 100 mg/d	0.55 (-0.70,1.80)	-0.10 (-1.57,1.35)	0.29 (-1.23,1.82)	—						
Gel 2%, 60 mg/d	0.11 (-1.11,1.33)	-0.54 (-1.99,0.90)	-0.15 (-1.66,1.34)	-0.44 (-2.18,1.31)	—					
Solution 2%, 60 mg/d	0.30 (-0.90,1.51)	-0.35 (-1.79,1.07)	0.04 (-1.43,1.53)	-0.25 (-1.99,1.50)	0.19 (-1.54,1.92)	—				
Oral TU, 160 mg/d	-0.47 (-1.41,0.43)	-1.12 (-2.34,0.05)	-0.73 (-2.02,0.51)	-1.03 (-2.60,0.52)	-0.59 (-2.14,0.95)	-0.78 (-2.31,0.73)	—			
IM TU, 1000 mg/10 wk	0.17 (-0.77,1.19)	-0.48 (-1.69,0.78)	-0.09 (-1.35,1.24)	-0.38 (-1.92,1.25)	0.06 (-1.47,1.66)	-0.13 (-1.63,1.46)	0.65 (-0.65,2.04)	—		
IM TU, 1000 mg/ 12 wk	0.21 (-0.36,0.76)	-0.44 (-1.40,0.49)	-0.05 (-1.10,0.96)	-0.34 (-1.72,1.02)	0.10 (-1.24,1.44)	-0.09 (-1.44,1.23)	0.68 (-0.29,1.68)	0.03 (-1.13,1.12)	—	
IM TE 250 mg/4wk	0.22 (-1.00,1.45)	-0.43 (-1.88,1.01)	-0.04 (-1.54,1.46)	-0.33 (-2.08,1.41)	0.11 (-1.63,1.84)	-0.08 (-1.80,1.62)	0.69 (-0.83,2.22)	0.04 (-1.57,1.57)	0.01 (-1.33,1.36)	—

Note: IM = intramuscular injection, TE = testosterone enanthate, TU = testosterone undecanoate.
*Random effects model. Analysis based on change from baseline. A positive SMD indicates improvement in erectile function. Significant changes are indicated by use of bold and colour (green indicates that the row treatment is significantly better than the column treatment, while red indicates that the row treatment is significantly worse than the column treatment). White indicates no significant difference between treatments.

eTable 8: Total testosterone level after 3 months of treatment – Bayesian network meta-analysis*

*Random effects model. Analysis is based on mean total testosterone level after treatment. A positive mean difference indicates a statistically significant improvement in total testosterone level. Significant changes are indicated by use of bold and colour (green indicates that the treatment is significantly better than the reference, while red indicates that the treatment is significantly worse than the reference). White indicates no significant difference between treatment and reference.

Treatment	Reference	Mean difference (95% credible intervals)
Patch 4.8 mg/d	Placebo	12.46(-3.49,28.17)
Patch 5 mg/d		**5.06(0.88,9.25)**
Gel 1% 50 mg/d		**6.54(3.51,9.65)**
Gel 1% 75 mg/d		7.48(-2.02,17.01)
Gel 1% 100 mg/d		**9.82(6.19,13.44)**
Oral TU 120 mg/d		4.31(-4.08,12.69)
Oral TU 160 mg/d		3.64(-4.69,11.86)
Testosterone pellets 1200 mg		6.40(-5.08,17.89)
IM TU 1000 mg/12 wk		**8.91(2.80,15.08)**
IM TE 100 mg/wk		**12.12(3.48,20.83)**
IM TE 200 mg/2wk		6.26(-2.80,15.34)
IM TE 250 mg/3wk		**12.78(1.28,24.21)**
IM TC 200 mg/2 wk		3.25(-6.32,12.89)
IM TC 200 mg/4 wk		1.73(-8.61,12.15)
Durateston, IM, 250 mg/4wk		2.13(-8.21,12.60)
Patch 5 mg/d	Patch 4.8 mg/d	-7.40(-23.71,9.17)
Gel 1% 50 mg/d		-5.91(-21.92,10.35)
Gel 1% 75 mg/d		-4.98(-23.37,13.63)
Gel 1% 100 mg/d		-2.64(-18.80,13.74)
Oral TU 120 mg/d		-8.15(-26.04,9.82)
Oral TU 160 mg/d		-8.82(-22.30,4.67)
Testosterone pellets 1200 mg		-6.06(-18.69,6.69)
IM TU 1000 mg/12 wk		-3.55(-20.42,13.57)
IM TE 100 mg/wk		-0.34(-18.30,17.61)
IM TE 200 mg/2wk		-6.20(-24.42,12.21)
IM TE 250 mg/3wk		0.32(-10.51,11.25)
IM TC 200 mg/2 wk		-9.21(-27.76,9.46)
IM TC 200 mg/4 wk		-10.72(-29.59,8.36)
Durateston, IM, 250 mg/4wk		-10.33(-29.25,8.69)
Gel 1% 50 mg/d	Patch 5 mg/d	1.48(-2.69,5.71)
Gel 1% 75 mg/d		2.41(-7.90,12.76)
Gel 1% 100 mg/d		**4.76(0.40,9.04)**
Oral TU 120 mg/d		-0.75(-10.16,8.55)

Oral TU 160 mg/d		-1.43(-10.82,7.80)
Testosterone pellets 1200 mg		1.34(-10.92,13.53)
IM TU 1000 mg/12 wk		3.85(-3.58,11.27)
IM TE 100 mg/wk		7.06(-2.53,16.60)
IM TE 200 mg/2wk		1.19(-8.83,11.18)
IM TE 250 mg/3wk		7.72(-4.58,19.84)
IM TC 200 mg/2 wk		-1.81(-12.35,8.73)
IM TC 200 mg/4 wk		-3.33(-14.50,7.86)
Durateston, IM, 250 mg/4wk		-2.94(-14.12,8.32)
Gel 1% 75 mg/d	Gel 1% 50 mg/d	0.93(-8.98,10.93)
Gel 1% 100 mg/d		3.27(-0.68,7.16)
Oral TU 120 mg/d		-2.23(-11.30,6.62)
Oral TU 160 mg/d		-2.91(-11.82,5.84)
Testosterone pellets 1200 mg		-0.14(-12.11,11.71)
IM TU 1000 mg/12 wk		2.37(-4.49,9.22)
IM TE 100 mg/wk		5.57(-3.60,14.72)
IM TE 200 mg/2wk		-0.29(-9.83,9.28)
IM TE 250 mg/3wk		6.24(-5.72,18.05)
IM TC 200 mg/2 wk		-3.30(-13.42,6.78)
IM TC 200 mg/4 wk		-4.81(-15.66,5.96)
Durateston, IM, 250 mg/4wk		-4.42(-15.28,6.46)
Gel 1% 100 mg/d	Gel 1% 75 mg/d	2.34(-7.87,12.46)
Oral TU 120 mg/d		-3.17(-15.86,9.38)
Oral TU 160 mg/d		-3.84(-16.49,8.72)
Testosterone pellets 1200 mg		-1.07(-15.98,13.79)
IM TU 1000 mg/12 wk		1.44(-9.92,12.73)
IM TE 100 mg/wk		4.64(-8.23,17.49)
IM TE 200 mg/2wk		-1.22(-14.30,11.90)
IM TE 250 mg/3wk		5.31(-9.66,20.08)
IM TC 200 mg/2 wk		-4.23(-17.84,9.24)
IM TC 200 mg/4 wk		-5.74(-19.84,8.38)
Durateston, IM, 250 mg/4wk		-5.35(-19.41,8.93)
Oral TU 120 mg/d	Gel 1% 100 mg/d	-5.51(-14.69,3.57)
Oral TU 160 mg/d		-6.18(-15.23,2.79)
Testosterone pellets 1200 mg		-3.41(-15.41,8.57)
IM TU 1000 mg/12 wk		-0.91(-8.03,6.24)
IM TE 100 mg/wk		2.30(-7.08,11.64)
IM TE 200 mg/2wk		-3.56(-13.34,6.30)
IM TE 250 mg/3wk		2.96(-9.16,14.85)
IM TC 200 mg/2 wk		-6.57(-16.82,3.69)
IM TC 200 mg/4 wk		-8.08(-19.02,2.89)
Durateston, IM, 250 mg/4wk		-7.69(-18.61,3.38)

Oral TU 160 mg/d	Oral TU 120 mg/d	-0.67(-12.46,11.10)
Testosterone pellets 1200 mg		2.09(-12.01,16.29)
IM TU 1000 mg/12 wk		4.60(-5.79,14.94)
IM TE 100 mg/wk		7.81(-4.20,19.92)
IM TE 200 mg/2wk		1.95(-10.36,14.39)
IM TE 250 mg/3wk		8.47(-5.65,22.61)
IM TC 200 mg/2 wk		-1.06(-13.92,11.70)
IM TC 200 mg/4 wk		-2.58(-16.00,10.91)
Durateston, IM, 250 mg/4wk		-2.18(-15.61,11.22)
Testosterone pellets 1200 mg	Oral TU 160 mg/d	2.77(-5.26,10.82)
IM TU 1000 mg/12 wk		5.28(-5.00,15.64)
IM TE 100 mg/wk		8.48(-3.53,20.45)
IM TE 200 mg/2wk		2.62(-9.56,14.98)
IM TE 250 mg/3wk		**9.15(1.17,17.13)**
IM TC 200 mg/2 wk		-0.39(-13.19,12.34)
IM TC 200 mg/4 wk		-1.90(-15.18,11.34)
Durateston, IM, 250 mg/4wk		-1.51(-14.84,11.86)
IM TU 1000 mg/12 wk	Testosterone pellets 1200 mg	2.51(-10.54,15.55)
IM TE 100 mg/wk		5.71(-8.62,19.97)
IM TE 200 mg/2wk		-0.15(-14.76,14.51)
IM TE 250 mg/3wk		6.38(-0.25,13.01)
IM TC 200 mg/2 wk		-3.16(-18.21,11.86)
IM TC 200 mg/4 wk		-4.67(-20.16,10.75)
Durateston, IM, 250 mg/4wk		-4.28(-19.96,11.21)
IM TE 100 mg/wk	IM TU 1000 mg/12 wk	3.21(-7.33,13.81)
IM TE 200 mg/2wk		-2.66(-13.63,8.30)
IM TE 250 mg/3wk		3.87(-9.22,16.79)
IM TC 200 mg/2 wk		-5.66(-17.05,5.71)
IM TC 200 mg/4 wk		-7.18(-15.50,1.16)
Durateston, IM, 250 mg/4wk		-6.79(-15.25,1.65)
IM TE 200 mg/2wk	IM TE 100 mg/wk	-5.86(-18.36,6.71)
IM TE 250 mg/3wk		0.66(-13.63,15.00)
IM TC 200 mg/2 wk		-8.87(-21.88,4.14)
IM TC 200 mg/4 wk		-10.38(-23.84,3.13)
Durateston, IM, 250 mg/4wk		-9.99(-23.47,3.48)
IM TE 250 mg/3wk	IM TE 200 mg/2wk	6.53(-8.23,21.04)
IM TC 200 mg/2 wk		-3.01(-16.17,10.25)
IM TC 200 mg/4 wk		-4.52(-18.16,9.20)
Durateston, IM, 250 mg/4wk		-4.13(-17.94,9.72)
IM TC 200 mg/2 wk	IM TE 250 mg/3wk	-9.53(-24.53,5.59)
IM TC 200 mg/4 wk		-11.05(-26.44,4.43)
Durateston, IM, 250 mg/4wk		-10.65(-26.22,4.95)

IM TC 200 mg/4 wk	IM TC 200 mg/2 wk	-1.51(-15.53,12.52)
Durateston, IM, 250 mg/4wk		-1.12(-15.17,13.08)
Durateston, IM, 250 mg/4wk	IM TC 200 mg/4 wk	0.39(-8.03,8.79)

eTable 9: Total testosterone level after 6 months of treatment – Bayesian network meta-analysis*

*Random effects model. Analysis based mean total testosterone level after treatment. A positive MD indicates a statistically significant improvement in total testosterone level. Significant changes are indicated by use of bold and colour (green indicates that the row treatment is significantly better than the column treatment, while red indicates that the row treatment is significantly worse than the column treatment). White indicates no significant difference between treatments.

Treatment	Reference	Mean difference (95% credible interval)
Patch 4.8 mg/d	Placebo	10.69(-1.17,22.73)
Patch 5 mg/d		**8.45(0.51,16.35)**
Gel 1% 50 mg/d		**7.94(4.36,11.49)**
Gel 1% 75 mg/d		5.76(-0.75,12.29)
Gel 1% 100 mg/d		**7.47(3.50,11.40)**
Gel 2% 60 mg/d		**19.80(13.59,26.00)**
Gel 2.5%, 125 mg/d		**12.13(2.00,22.09)**
Gel (scrotal) 2.5%, 25 mg/d		7.89(-2.18,17.86)
Oral TU 120-160 mg/d		5.68(-0.52,11.88)
Oral TU 160 mg/d		1.84(-2.44,6.10)
Testosterone pellets 1200 mg		4.69(-2.86,12.17)
IM TU 1000 mg/12 wk		**8.07(3.71,12.46)**
IM TE 150 mg/2wk		**12.72(5.10,20.29)**
IM TE 200 mg/2wk		**10.10(2.68,17.61)**
IM TE 250 mg/3wk		**11.02(3.59,18.55)**
IM TE 300 mg/3wk		**18.25(10.92,25.60)**
IM TE 50-400 mg/1-2 wk		**14.74(4.55,25.01)**
IM TC 200 mg/2 wk		3.21(-4.73,11.12)
Patch 5 mg/d	Patch 4.8 mg/d	-2.24(-16.71,11.98)
Gel 1% 50 mg/d		-2.75(-15.42,9.56)
Gel 1% 75 mg/d		-4.94(-18.49,8.60)
Gel 1% 100 mg/d		-3.22(-15.94,9.31)
Gel 2% 60 mg/d		9.11(-4.41,22.45)
Gel 2.5%, 125 mg/d		1.44(-14.32,16.85)
Gel (scrotal) 2.5%, 25 mg/d		-2.80(-18.53,12.61)
Oral TU 120-160 mg/d		-5.01(-18.65,8.35)
Oral TU 160 mg/d		-8.85(-20.06,2.21)
Testosterone pellets 1200 mg		-6.01(-16.78,4.72)

IM TU 1000 mg/12 wk		-2.62(-14.99,9.53)
IM TE 150 mg/2wk		2.03(-12.24,16.16)
IM TE 200 mg/2wk		-0.59(-14.66,13.38)
IM TE 250 mg/3wk		0.33(-9.00,9.68)
IM TE 300 mg/3wk		7.56(-6.50,21.52)
IM TE 50-400 mg/1-2 wk		4.05(-11.55,19.64)
IM TC 200 mg/2 wk		-7.49(-21.86,6.80)
Gel 1% 50 mg/d	Patch 5 mg/d	-0.51(-9.17,8.26)
Gel 1% 75 mg/d		-2.70(-12.88,7.57)
Gel 1% 100 mg/d		-0.98(-9.71,7.83)
Gel 2% 60 mg/d		**11.35(1.38,21.45)**
Gel 2.5%, 125 mg/d		3.68(-2.57,9.89)
Gel (scrotal) 2.5%, 25 mg/d		-0.56(-6.82,5.64)
Oral TU 120-160 mg/d		-2.77(-12.83,7.29)
Oral TU 160 mg/d		-6.61(-15.60,2.37)
Testosterone pellets 1200 mg		-3.76(-14.64,7.17)
IM TU 1000 mg/12 wk		-0.38(-9.40,8.59)
IM TE 150 mg/2wk		4.27(-6.77,15.19)
IM TE 200 mg/2wk		1.65(-9.12,12.46)
IM TE 250 mg/3wk		2.57(-8.35,13.50)
IM TE 300 mg/3wk		9.80(-1.00,20.57)
IM TE 50-400 mg/1-2 wk		6.29(-6.46,19.33)
IM TC 200 mg/2 wk		-5.25(-16.35,5.95)
Gel 1% 75 mg/d	Gel 1% 50 mg/d	-2.19(-9.54,5.26)
Gel 1% 100 mg/d		-0.47(-5.79,4.89)
Gel 2% 60 mg/d		**11.86(4.68,19.05)**
Gel 2.5%, 125 mg/d		4.19(-6.52,14.80)
Gel (scrotal) 2.5%, 25 mg/d		-0.05(-10.72,10.61)
Oral TU 120-160 mg/d		-2.26(-9.34,4.96)
Oral TU 160 mg/d		**-6.10(-11.64,-0.46)**
Testosterone pellets 1200 mg		-3.25(-11.55,5.08)
IM TU 1000 mg/12 wk		0.13(-5.49,5.79)
IM TE 150 mg/2wk		4.78(-3.58,13.19)
IM TE 200 mg/2wk		2.16(-5.97,10.48)
IM TE 250 mg/3wk		3.08(-5.14,11.45)
IM TE 300 mg/3wk		**10.31(2.17,18.53)**
IM TE 50-400 mg/1-2 wk		6.80(-4.00,17.62)
IM TC 200 mg/2 wk		-4.74(-13.42,3.94)
Gel 1% 100 mg/d	Gel 1% 75 mg/d	1.71(-5.94,9.34)
Gel 2% 60 mg/d		**14.04(5.05,22.97)**
Gel 2.5%, 125 mg/d		6.37(-5.71,18.31)
Gel (scrotal) 2.5%, 25 mg/d		2.14(-9.89,14.03)

Oral TU 120-160 mg/d		-0.07(-9.16,8.90)
Oral TU 160 mg/d		-3.91(-11.78,3.88)
Testosterone pellets 1200 mg		-1.07(-10.98,8.82)
IM TU 1000 mg/12 wk		2.31(-5.63,10.19)
IM TE 150 mg/2wk		6.96(-3.13,17.01)
IM TE 200 mg/2wk		4.35(-5.60,14.23)
IM TE 250 mg/3wk		5.26(-4.59,15.19)
IM TE 300 mg/3wk		**12.50(2.64,22.31)**
IM TE 50-400 mg/1-2 wk		8.99(-3.00,21.03)
IM TC 200 mg/2 wk		-2.55(-12.74,7.68)
Gel 2% 60 mg/d	Gel 1% 100 mg/d	**12.33(5.03,19.71)**
Gel 2.5%, 125 mg/d		4.66(-6.17,15.34)
Gel (scrotal) 2.5%, 25 mg/d		0.42(-10.35,11.17)
Oral TU 120-160 mg/d		-1.79(-9.10,5.58)
Oral TU 160 mg/d		-5.63(-11.50,0.28)
Testosterone pellets 1200 mg		-2.78(-11.34,5.78)
IM TU 1000 mg/12 wk		0.60(-5.31,6.53)
IM TE 150 mg/2wk		5.25(-3.38,13.81)
IM TE 200 mg/2wk		2.63(-5.77,11.14)
IM TE 250 mg/3wk		3.55(-4.93,12.14)
IM TE 300 mg/3wk		**10.78(2.42,19.14)**
IM TE 50-400 mg/1-2 wk		7.28(-3.63,18.18)
IM TC 200 mg/2 wk		-4.27(-13.06,4.61)
Gel 2.5%, 125 mg/d	Gel 2% 60 mg/d	-7.67(-19.47,3.96)
Gel (scrotal) 2.5%, 25 mg/d		**-11.91(-23.69,-0.16)**
Oral TU 120-160 mg/d		**-14.11(-22.91,-5.33)**
Oral TU 160 mg/d		**-17.96(-25.47,-10.36)**
Testosterone pellets 1200 mg		**-15.11(-24.85,-5.36)**
IM TU 1000 mg/12 wk		**-11.73(-19.31,-4.11)**
IM TE 150 mg/2wk		-7.08(-16.88,2.74)
IM TE 200 mg/2wk		**-9.70(-19.39,-0.03)**
IM TE 250 mg/3wk		-8.78(-18.41,1.02)
IM TE 300 mg/3wk		-1.55(-11.11,8.12)
IM TE 50-400 mg/1-2 wk		-5.05(-16.93,6.87)
IM TC 200 mg/2 wk		**-16.59(-26.63,-6.52)**
Gel (scrotal) 2.5%, 25 mg/d	Gel 2.5%, 125 mg/d	-4.24(-10.53,1.98)
Oral TU 120-160 mg/d		-6.45(-18.26,5.33)
Oral TU 160 mg/d		-10.29(-21.22,0.66)
Testosterone pellets 1200 mg		-7.44(-19.87,5.14)
IM TU 1000 mg/12 wk		-4.06(-14.99,6.89)
IM TE 150 mg/2wk		0.59(-12.00,13.23)
IM TE 200 mg/2wk		-2.03(-14.56,10.54)

IM TE 250 mg/3wk		-1.11(-13.58,11.45)
IM TE 300 mg/3wk		6.12(-6.29,18.59)
IM TE 50-400 mg/1-2 wk		2.62(-11.57,17.04)
IM TC 200 mg/2 wk		-8.92(-21.55,3.89)
Oral TU 120-160 mg/d	Gel (scrotal) 2.5%, 25 mg/d	-2.21(-14.01,9.62)
Oral TU 160 mg/d		-6.05(-16.91,4.92)
Testosterone pellets 1200 mg		-3.21(-15.72,9.40)
IM TU 1000 mg/12 wk		0.18(-10.74,11.14)
IM TE 150 mg/2wk		4.82(-7.68,17.43)
IM TE 200 mg/2wk		2.21(-10.23,14.82)
IM TE 250 mg/3wk		3.13(-9.48,15.73)
IM TE 300 mg/3wk		10.36(-2.02,22.83)
IM TE 50-400 mg/1-2 wk		6.85(-7.36,21.24)
IM TC 200 mg/2 wk		-4.69(-17.36,8.11)
Oral TU 160 mg/d	Oral TU 120-160 mg/d	-3.84(-11.38,3.69)
Testosterone pellets 1200 mg		-1.00(-10.73,8.75)
IM TU 1000 mg/12 wk		2.39(-5.28,10.08)
IM TE 150 mg/2wk		7.03(-2.78,16.80)
IM TE 200 mg/2wk		4.42(-5.26,14.13)
IM TE 250 mg/3wk		5.33(-4.33,15.11)
IM TE 300 mg/3wk		**12.57(2.91,22.18)**
IM TE 50-400 mg/1-2 wk		9.06(-2.84,21.05)
IM TC 200 mg/2 wk		-2.48(-12.54,7.57)
Testosterone pellets 1200 mg	Oral TU 160 mg/d	2.84(-3.35,9.02)
IM TU 1000 mg/12 wk		**6.23(1.04,11.41)**
IM TE 150 mg/2wk		**10.87(2.16,19.57)**
IM TE 200 mg/2wk		8.26(-0.33,16.82)
IM TE 250 mg/3wk		**9.18(3.03,15.42)**
IM TE 300 mg/3wk		**16.41(7.93,25.00)**
IM TE 50-400 mg/1-2 wk		**12.90(1.81,23.95)**
IM TC 200 mg/2 wk		1.36(-7.75,10.40)
IM TU 1000 mg/12 wk	Testosterone pellets 1200 mg	3.38(-4.67,11.50)
IM TE 150 mg/2wk		8.03(-2.77,18.77)
IM TE 200 mg/2wk		5.42(-5.01,16.06)
IM TE 250 mg/3wk		**6.33(0.97,11.73)**
IM TE 300 mg/3wk		**13.57(3.19,24.08)**
IM TE 50-400 mg/1-2 wk		10.06(-2.53,22.73)
IM TC 200 mg/2 wk		-1.48(-12.38,9.46)
IM TE 150 mg/2wk	IM TU 1000 mg/12 wk	4.65(-4.13,13.37)
IM TE 200 mg/2wk		2.03(-6.70,10.69)
IM TE 250 mg/3wk		2.95(-5.08,11.11)
IM TE 300 mg/3wk		**10.18(1.58,18.75)**

IM TE 50-400 mg/1-2 wk		6.68(-4.45,17.75)
IM TC 200 mg/2 wk		-4.86(-13.89,4.19)
IM TE 200 mg/2wk	IM TE 150 mg/2wk	-2.61(-13.28,8.17)
IM TE 250 mg/3wk		-1.70(-12.39,9.20)
IM TE 300 mg/3wk		5.54(-5.10,16.15)
IM TE 50-400 mg/1-2 wk		2.03(-10.78,14.82)
IM TC 200 mg/2 wk		-9.51(-20.53,1.51)
IM TE 250 mg/3wk	IM TE 200 mg/2wk	0.92(-9.64,11.36)
IM TE 300 mg/3wk		8.15(-2.38,18.61)
IM TE 50-400 mg/1-2 wk		4.64(-7.93,17.27)
IM TC 200 mg/2 wk		-6.90(-17.80,4.00)
IM TE 300 mg/3wk	IM TE 250 mg/3wk	7.23(-3.23,17.75)
IM TE 50-400 mg/1-2 wk		3.73(-8.88,16.28)
IM TC 200 mg/2 wk	IM TE 300 mg/3wk	-7.81(-18.75,3.15)
IM TE 50-400 mg/1-2 wk		-3.51(-16.11,8.94)
IM TC 200 mg/2 wk		**-15.05(-25.92,-4.21)**
IM TC 200 mg/2 wk	IM TE 50-400 mg/1-2 wk	-11.54(-24.57,1.32)

eTable 10: Total testosterone levels at the end of treatment – Bayesian network meta-analysis*

*Random effects model. Analysis is based on mean total testosterone level after treatment. A positive mean difference indicates a statistically significant improvement in total testosterone level. Significant changes are indicated by use of bold and colour (green indicates that the treatment is significantly better than the reference, while red indicates that the treatment is significantly worse than the reference). White indicates no significant difference between treatment and reference.

Treatment	Reference	Mean difference (95% credible interval)
Patch 4.8 mg/d	Placebo	8.00(-3.40,19.24)
Patch 5 mg/d		4.74(1.65,7.84)
Gel 1% 5 mg/d		3.66(-4.21,11.57)
Gel 1% 50 mg/d		6.54(4.27,8.85)
Gel 1% 75 mg/d		6.49(0.92,12.04)
Gel 1% 100 mg/d		9.76(6.92,12.61)
Gel 2% 60 mg/d		19.76(12.66,26.85)
Gel 2.5%, 125 mg/d		8.44(0.75,16.16)
Gel (scrotal) 2.5%, 25 mg/d		4.19(-3.53,11.91)
Solution 2%, 60 mg/d		8.47(0.47,16.40)
Oral TU 120 mg/d		4.32(-2.98,11.63)
Oral TU 160 mg/d		1.40(-2.28,5.08)
Oral TU 120-160 mg/d		5.69(-1.33,12.73)
Testosterone pellets 1200 mg		2.77(-3.99,9.50)
IM TU 1000 mg/9 wk		16.32(6.99,25.58)
IM TU 1000 mg/10 wk		5.70(0.07,11.29)

IM TU 1000 mg/12 wk		8.45(5.99,10.90)
IM TE 100 mg/wk		9.52(4.08,14.91)
IM TE 125 mg/wk		6.76(-3.38,16.87)
IM TE 150 mg/2wk		12.71(4.36,21.09)
IM TE 200 mg/2wk		10.67(5.96,15.35)
IM TE 250 mg/3wk		8.33(2.98,13.71)
IM TE 300 mg/3wk		18.26(9.96,26.49)
IM TE 50-400 mg/1-2 wk		14.74(3.91,25.46)
IM TC 200 mg/2 wk		3.20(-5.49,11.85)
IM TC 200 mg/4 wk		1.30(-6.39,8.98)
IM TC 250 mg/2wk		9.73(1.91,17.51)
Durateston, IM, 250 mg/4wk		1.67(-6.17,9.42)
Patch 5 mg/d	Patch 4.8 mg/d	-3.26(-14.89,8.56)
Gel 1% 5 mg/d		-4.34(-18.04,9.54)
Gel 1% 50 mg/d		-1.46(-12.93,10.15)
Gel 1% 75 mg/d		-1.51(-14.10,11.24)
Gel 1% 100 mg/d		1.76(-9.83,13.46)
Gel 2% 60 mg/d		11.76(-1.57,25.26)
Gel 2.5%, 125 mg/d		0.44(-13.20,14.18)
Gel (scrotal) 2.5%, 25 mg/d		-3.81(-17.47,9.95)
Solution 2%, 60 mg/d		0.47(-13.38,14.35)
Oral TU 120 mg/d		-3.68(-17.02,9.84)
Oral TU 160 mg/d		-6.60(-17.82,4.81)
Oral TU 120-160 mg/d		-2.31(-15.69,11.06)
Testosterone pellets 1200 mg		-5.23(-16.69,6.32)
IM TU 1000 mg/9 wk		8.32(-4.22,20.91)
IM TU 1000 mg/10 wk		-2.30(-14.89,10.43)
IM TU 1000 mg/12 wk		0.45(-11.02,12.05)
IM TE 100 mg/wk		1.52(-10.96,14.13)
IM TE 125 mg/wk		-1.24(-16.45,13.89)
IM TE 150 mg/2wk		4.71(-9.35,18.84)
IM TE 200 mg/2wk		2.67(-9.60,14.94)
IM TE 250 mg/3wk		0.33(-9.63,10.45)
IM TE 300 mg/3wk		10.26(-3.79,24.37)
IM TE 50-400 mg/1-2 wk		6.75(-8.90,22.49)
IM TC 200 mg/2 wk		-4.80(-19.10,9.52)
IM TC 200 mg/4 wk		-6.70(-20.28,7.08)
IM TC 250 mg/2wk		1.73(-11.91,15.43)
Durateston, IM, 250 mg/4wk		-6.33(-20.01,7.57)
Gel 1% 5 mg/d	Patch 5 mg/d	-1.08(-9.49,7.42)
Gel 1% 50 mg/d		1.80(-1.49,5.16)
Gel 1% 75 mg/d		1.76(-4.64,8.14)

Gel 1% 100 mg/d		5.02(1.52,8.49)
Gel 2% 60 mg/d		15.02(7.19,22.80)
Gel 2.5%, 125 mg/d		3.70(-3.39,10.73)
Gel (scrotal) 2.5%, 25 mg/d		-0.55(-7.68,6.53)
Solution 2%, 60 mg/d		3.73(-4.85,12.32)
Oral TU 120 mg/d		-0.41(-8.32,7.44)
Oral TU 160 mg/d		-3.33(-8.17,1.43)
Oral TU 120-160 mg/d		0.95(-6.78,8.61)
Testosterone pellets 1200 mg		-1.97(-9.42,5.39)
IM TU 1000 mg/9 wk		11.58(1.73,21.42)
IM TU 1000 mg/10 wk		0.96(-5.42,7.38)
IM TU 1000 mg/12 wk		3.72(-0.31,7.66)
IM TE 100 mg/wk		4.78(-1.44,10.97)
IM TE 125 mg/wk		2.02(-8.51,12.56)
IM TE 150 mg/2wk		7.97(-0.95,16.86)
IM TE 200 mg/2wk		5.93(0.94,10.87)
IM TE 250 mg/3wk		3.59(-2.64,9.81)
IM TE 300 mg/3wk		13.52(4.66,22.31)
IM TE 50-400 mg/1-2 wk		10.01(-1.36,21.18)
IM TC 200 mg/2 wk		-1.54(-10.74,7.65)
IM TC 200 mg/4 wk		-3.44(-11.77,4.80)
IM TC 250 mg/2wk		4.99(-3.43,13.41)
Durateston, IM, 250 mg/4wk		-3.07(-11.56,5.28)
Gel 1% 50 mg/d	Gel 1% 5 mg/d	2.88(-5.34,11.08)
Gel 1% 75 mg/d		2.83(-6.84,12.54)
Gel 1% 100 mg/d		6.10(-2.30,14.48)
Gel 2% 60 mg/d		16.10(5.47,26.65)
Gel 2.5%, 125 mg/d		4.78(-6.22,15.83)
Gel (scrotal) 2.5%, 25 mg/d		0.53(-10.48,11.48)
Solution 2%, 60 mg/d		4.81(-6.33,15.99)
Oral TU 120 mg/d		0.66(-9.98,11.41)
Oral TU 160 mg/d		-2.26(-10.97,6.42)
Oral TU 120-160 mg/d		2.02(-8.54,12.63)
Testosterone pellets 1200 mg		-0.89(-11.28,9.45)
IM TU 1000 mg/9 wk		12.66(0.32,24.84)
IM TU 1000 mg/10 wk		2.04(-7.64,11.75)
IM TU 1000 mg/12 wk		4.79(-3.47,12.95)
IM TE 100 mg/wk		5.86(-3.72,15.40)
IM TE 125 mg/wk		3.10(-9.72,15.94)
IM TE 150 mg/2wk		9.05(-2.41,20.56)
IM TE 200 mg/2wk		7.01(-2.27,16.13)
IM TE 250 mg/3wk		4.67(-4.87,14.18)

IM TE 300 mg/3wk		14.60(3.17,26.00)
IM TE 50-400 mg/1-2 wk		11.08(-2.35,24.44)
IM TC 200 mg/2 wk		-0.46(-12.22,11.21)
IM TC 200 mg/4 wk		-2.37(-13.33,8.57)
IM TC 250 mg/2wk		6.07(-5.05,17.18)
Durateston, IM, 250 mg/4wk		-1.99(-13.08,9.06)
Gel 1% 75 mg/d	Gel 1% 50 mg/d	-0.05(-6.06,5.96)
Gel 1% 100 mg/d		3.22(0.05,6.36)
Gel 2% 60 mg/d		13.22(5.72,20.65)
Gel 2.5%, 125 mg/d		1.90(-5.89,9.68)
Gel (scrotal) 2.5%, 25 mg/d		-2.35(-10.23,5.47)
Solution 2%, 60 mg/d		1.93(-6.45,10.21)
Oral TU 120 mg/d		-2.22(-9.89,5.36)
Oral TU 160 mg/d		-5.14(-9.50,-0.83)
Oral TU 120-160 mg/d		-0.86(-8.26,6.53)
Testosterone pellets 1200 mg		-3.77(-10.93,3.32)
IM TU 1000 mg/9 wk		9.78(0.12,19.31)
IM TU 1000 mg/10 wk		-0.84(-6.93,5.22)
IM TU 1000 mg/12 wk		1.91(-1.49,5.22)
IM TE 100 mg/wk		2.98(-2.97,8.82)
IM TE 125 mg/wk		0.22(-10.17,10.56)
IM TE 150 mg/2wk		6.17(-2.50,14.84)
IM TE 200 mg/2wk		4.13(-0.98,9.17)
IM TE 250 mg/3wk		1.79(-4.11,7.62)
IM TE 300 mg/3wk		11.72(3.13,20.20)
IM TE 50-400 mg/1-2 wk		8.20(-2.93,19.12)
IM TC 200 mg/2 wk		-3.34(-12.34,5.62)
IM TC 200 mg/4 wk		-5.25(-13.24,2.71)
IM TC 250 mg/2wk		3.19(-4.96,11.30)
Durateston, IM, 250 mg/4wk		-4.87(-13.08,3.23)
Gel 1% 100 mg/d	Gel 1% 75 mg/d	3.26(-3.00,9.49)
Gel 2% 60 mg/d		13.27(4.21,22.29)
Gel 2.5%, 125 mg/d		1.95(-7.52,11.42)
Gel (scrotal) 2.5%, 25 mg/d		-2.30(-11.80,7.19)
Solution 2%, 60 mg/d		1.98(-7.79,11.68)
Oral TU 120 mg/d		-2.17(-11.46,7.10)
Oral TU 160 mg/d		-5.09(-11.81,1.62)
Oral TU 120-160 mg/d		-0.81(-9.76,8.21)
Testosterone pellets 1200 mg		-3.72(-12.49,5.06)
IM TU 1000 mg/9 wk		9.83(-1.12,20.61)
IM TU 1000 mg/10 wk		-0.79(-8.71,7.09)
IM TU 1000 mg/12 wk		1.96(-4.14,8.02)

IM TE 100 mg/wk		3.03(-4.78,10.84)
IM TE 125 mg/wk		0.27(-11.29,11.76)
IM TE 150 mg/2wk		6.21(-3.81,16.26)
IM TE 200 mg/2wk		4.18(-3.13,11.49)
IM TE 250 mg/3wk		1.84(-5.91,9.60)
IM TE 300 mg/3wk		11.76(1.77,21.71)
IM TE 50-400 mg/1-2 wk		8.25(-3.95,20.40)
IM TC 200 mg/2 wk		-3.30(-13.57,7.03)
IM TC 200 mg/4 wk		-5.20(-14.75,4.38)
IM TC 250 mg/2wk		3.24(-6.31,12.84)
Durateston, IM, 250 mg/4wk		-4.82(-14.54,4.73)
Gel 2% 60 mg/d	Gel 1% 100 mg/d	10.00(2.31,17.65)
Gel 2.5%, 125 mg/d		-1.32(-9.14,6.53)
Gel (scrotal) 2.5%, 25 mg/d		-5.57(-13.46,2.30)
Solution 2%, 60 mg/d		-1.29(-9.81,7.12)
Oral TU 120 mg/d		-5.43(-13.31,2.41)
Oral TU 160 mg/d		-8.35(-13.01,-3.72)
Oral TU 120-160 mg/d		-4.07(-11.66,3.46)
Testosterone pellets 1200 mg		-6.98(-14.31,0.32)
IM TU 1000 mg/9 wk		6.56(-3.21,16.30)
IM TU 1000 mg/10 wk		-4.05(-10.36,2.25)
IM TU 1000 mg/12 wk		-1.30(-5.08,2.39)
IM TE 100 mg/wk		-0.24(-6.33,5.86)
IM TE 125 mg/wk		-3.00(-13.56,7.45)
IM TE 150 mg/2wk		2.95(-5.87,11.76)
IM TE 200 mg/2wk		0.91(-4.37,6.24)
IM TE 250 mg/3wk		-1.43(-7.51,4.70)
IM TE 300 mg/3wk		8.50(-0.26,17.19)
IM TE 50-400 mg/1-2 wk		4.99(-6.29,16.05)
IM TC 200 mg/2 wk		-6.56(-15.67,2.62)
IM TC 200 mg/4 wk		-8.46(-16.58,-0.35)
IM TC 250 mg/2wk		-0.03(-8.32,8.21)
Durateston, IM, 250 mg/4wk		-8.09(-16.37,0.19)
Gel 2.5%, 125 mg/d	Gel 2% 60 mg/d	-11.32(-21.81,-0.76)
Gel (scrotal) 2.5%, 25 mg/d		-15.57(-26.01,-5.14)
Solution 2%, 60 mg/d		-11.29(-22.04,-0.61)
Oral TU 120 mg/d		-15.44(-25.55,-5.26)
Oral TU 160 mg/d		-18.36(-26.38,-10.40)
Oral TU 120-160 mg/d		-14.08(-24.01,-4.07)
Testosterone pellets 1200 mg		-16.99(-26.76,-7.21)
IM TU 1000 mg/9 wk		-3.44(-15.22,8.28)
IM TU 1000 mg/10 wk		-14.06(-23.21,-4.99)

IM TU 1000 mg/12 wk		-11.31(-18.81,-3.79)
IM TE 100 mg/wk		-10.24(-19.18,-1.26)
IM TE 125 mg/wk		-13.00(-25.43,-0.67)
IM TE 150 mg/2wk		-7.05(-18.02,3.89)
IM TE 200 mg/2wk		-9.09(-17.56,-0.59)
IM TE 250 mg/3wk		-11.43(-20.28,-2.55)
IM TE 300 mg/3wk		-1.50(-12.41,9.29)
IM TE 50-400 mg/1-2 wk		-5.02(-17.95,7.94)
IM TC 200 mg/2 wk		-16.56(-27.65,-5.38)
IM TC 200 mg/4 wk		-18.47(-28.79,-7.99)
IM TC 250 mg/2wk		-10.03(-20.60,0.55)
Durateston, IM, 250 mg/4wk		-18.09(-28.55,-7.51)
Gel (scrotal) 2.5%, 25 mg/d	Gel 2.5%, 125 mg/d	-4.25(-11.32,2.85)
Solution 2%, 60 mg/d		0.03(-11.01,11.05)
Oral TU 120 mg/d		-4.11(-14.77,6.43)
Oral TU 160 mg/d		-7.03(-15.56,1.49)
Oral TU 120-160 mg/d		-2.75(-13.20,7.62)
Testosterone pellets 1200 mg		-5.67(-15.93,4.50)
IM TU 1000 mg/9 wk		7.88(-4.23,19.98)
IM TU 1000 mg/10 wk		-2.74(-12.35,6.74)
IM TU 1000 mg/12 wk		0.02(-8.05,8.09)
IM TE 100 mg/wk		1.08(-8.38,10.49)
IM TE 125 mg/wk		-1.68(-14.40,11.04)
IM TE 150 mg/2wk		4.27(-7.05,15.61)
IM TE 200 mg/2wk		2.23(-6.41,10.86)
IM TE 250 mg/3wk		-0.11(-9.59,9.27)
IM TE 300 mg/3wk		9.82(-1.46,21.10)
IM TE 50-400 mg/1-2 wk		6.31(-7.08,19.61)
IM TC 200 mg/2 wk		-5.24(-16.86,6.39)
IM TC 200 mg/4 wk		-7.14(-18.05,3.70)
IM TC 250 mg/2wk		1.29(-9.68,12.14)
Durateston, IM, 250 mg/4wk		-6.77(-17.77,4.17)
Solution 2%, 60 mg/d	Gel (scrotal) 2.5%, 25 mg/d	4.28(-6.76,15.29)
Oral TU 120 mg/d		0.13(-10.41,10.69)
Oral TU 160 mg/d		-2.79(-11.32,5.78)
Oral TU 120-160 mg/d		1.49(-8.95,11.85)
Testosterone pellets 1200 mg		-1.42(-11.69,8.77)
IM TU 1000 mg/9 wk		12.13(-0.05,24.28)
IM TU 1000 mg/10 wk		1.51(-8.10,11.01)
IM TU 1000 mg/12 wk		4.26(-3.85,12.36)
IM TE 100 mg/wk		5.33(-4.13,14.73)
IM TE 125 mg/wk		2.57(-10.20,15.23)

IM TE 150 mg/2wk		8.52(-2.86,19.92)
IM TE 200 mg/2wk		6.48(-2.21,15.12)
IM TE 250 mg/3wk		4.14(-5.23,13.54)
IM TE 300 mg/3wk		14.07(2.81,25.31)
IM TE 50-400 mg/1-2 wk		10.55(-2.91,23.84)
IM TC 200 mg/2 wk		-0.99(-12.60,10.58)
IM TC 200 mg/4 wk		-2.90(-13.82,8.03)
IM TC 250 mg/2wk		5.54(-5.44,16.60)
Durateston, IM, 250 mg/4wk		-2.52(-13.52,8.43)
Oral TU 120 mg/d	Solution 2%, 60 mg/d	-4.15(-14.97,6.71)
Oral TU 160 mg/d		-7.07(-15.82,1.75)
Oral TU 120-160 mg/d		-2.79(-13.42,7.91)
Testosterone pellets 1200 mg		-5.70(-16.19,4.77)
IM TU 1000 mg/9 wk		7.85(-4.39,20.17)
IM TU 1000 mg/10 wk		-2.77(-12.56,7.00)
IM TU 1000 mg/12 wk		-0.02(-8.34,8.36)
IM TE 100 mg/wk		1.05(-8.64,10.74)
IM TE 125 mg/wk		-1.71(-14.70,11.26)
IM TE 150 mg/2wk		4.24(-7.33,15.76)
IM TE 200 mg/2wk		2.20(-6.98,11.47)
IM TE 250 mg/3wk		-0.14(-9.75,9.50)
IM TE 300 mg/3wk		9.79(-1.75,21.38)
IM TE 50-400 mg/1-2 wk		6.27(-7.18,19.70)
IM TC 200 mg/2 wk		-5.27(-17.13,6.58)
IM TC 200 mg/4 wk		-7.17(-18.19,4.01)
IM TC 250 mg/2wk		1.26(-9.92,12.47)
Durateston, IM, 250 mg/4wk		-6.80(-17.95,4.39)
Oral TU 160 mg/d	Oral TU 120 mg/d	-2.92(-11.18,5.30)
Oral TU 120-160 mg/d		1.36(-8.75,11.51)
Testosterone pellets 1200 mg		-1.55(-11.47,8.35)
IM TU 1000 mg/9 wk		11.99(0.22,23.80)
IM TU 1000 mg/10 wk		1.38(-7.80,10.65)
IM TU 1000 mg/12 wk		4.13(-3.60,11.79)
IM TE 100 mg/wk		5.20(-3.98,14.29)
IM TE 125 mg/wk		2.44(-10.06,15.00)
IM TE 150 mg/2wk		8.38(-2.65,19.47)
IM TE 200 mg/2wk		6.35(-2.24,15.06)
IM TE 250 mg/3wk		4.01(-5.04,13.13)
IM TE 300 mg/3wk		13.93(2.85,24.90)
IM TE 50-400 mg/1-2 wk		10.42(-2.47,23.36)
IM TC 200 mg/2 wk		-1.13(-12.50,10.16)
IM TC 200 mg/4 wk		-3.03(-13.54,7.52)

IM TC 250 mg/2wk		5.41(-5.24,16.03)
Durateston, IM, 250 mg/4wk		-2.65(-13.24,7.90)
Oral TU 120-160 mg/d	Oral TU 160 mg/d	4.28(-3.65,12.24)
Testosterone pellets 1200 mg		1.37(-5.02,7.65)
IM TU 1000 mg/9 wk		14.91(5.60,24.22)
IM TU 1000 mg/10 wk		4.30(-2.44,10.98)
IM TU 1000 mg/12 wk		7.05(2.88,11.22)
IM TE 100 mg/wk		8.12(1.58,14.65)
IM TE 125 mg/wk		5.36(-5.44,16.14)
IM TE 150 mg/2wk		11.30(2.17,20.50)
IM TE 200 mg/2wk		9.27(3.31,15.24)
IM TE 250 mg/3wk		6.93(1.62,12.24)
IM TE 300 mg/3wk		16.85(7.78,25.85)
IM TE 50-400 mg/1-2 wk		13.34(1.90,24.69)
IM TC 200 mg/2 wk		1.79(-7.65,11.19)
IM TC 200 mg/4 wk		-0.11(-8.45,8.32)
IM TC 250 mg/2wk		8.33(-0.32,16.90)
Durateston, IM, 250 mg/4wk		0.27(-8.25,8.73)
Testosterone pellets 1200 mg	Oral TU 120-160 mg/d	-2.91(-12.66,6.81)
IM TU 1000 mg/9 wk		10.63(-1.05,22.19)
IM TU 1000 mg/10 wk		0.02(-8.97,9.02)
IM TU 1000 mg/12 wk		2.77(-4.70,10.19)
IM TE 100 mg/wk		3.83(-5.07,12.72)
IM TE 125 mg/wk		1.08(-11.31,13.34)
IM TE 150 mg/2wk		7.02(-3.93,18.04)
IM TE 200 mg/2wk		4.99(-3.53,13.53)
IM TE 250 mg/3wk		2.65(-6.16,11.47)
IM TE 300 mg/3wk		12.57(1.68,23.38)
IM TE 50-400 mg/1-2 wk		9.06(-3.94,21.88)
IM TC 200 mg/2 wk		-2.49(-13.64,8.66)
IM TC 200 mg/4 wk		-4.39(-14.76,6.03)
IM TC 250 mg/2wk		4.05(-6.43,14.57)
Durateston, IM, 250 mg/4wk		-4.02(-14.52,6.43)
IM TU 1000 mg/9 wk	Testosterone pellets 1200 mg	13.55(3.98,23.17)
IM TU 1000 mg/10 wk		2.93(-5.76,11.79)
IM TU 1000 mg/12 wk		5.68(-1.39,12.77)
IM TE 100 mg/wk		6.75(-1.86,15.41)
IM TE 125 mg/wk		3.99(-8.13,16.03)
IM TE 150 mg/2wk		9.93(-0.73,20.72)
IM TE 200 mg/2wk		7.90(-0.28,16.12)
IM TE 250 mg/3wk		5.56(-0.16,11.31)
IM TE 300 mg/3wk		15.48(4.84,26.11)

IM TE 50-400 mg/1-2 wk		11.97(-0.87,24.56)
IM TC 200 mg/2 wk		0.43(-10.60,11.33)
IM TC 200 mg/4 wk		-1.48(-11.65,8.68)
IM TC 250 mg/2wk		6.96(-3.27,17.22)
Durateston, IM, 250 mg/4wk		-1.10(-11.31,9.12)
IM TU 1000 mg/10 wk	IM TU 1000 mg/9 wk	-10.62(-21.47,0.34)
IM TU 1000 mg/12 wk		-7.87(-17.42,1.71)
IM TE 100 mg/wk		-6.80(-17.58,3.97)
IM TE 125 mg/wk		-9.56(-23.43,4.23)
IM TE 150 mg/2wk		-3.61(-16.13,8.87)
IM TE 200 mg/2wk		-5.65(-16.09,4.77)
IM TE 250 mg/3wk		-7.99(-15.63,-0.43)
IM TE 300 mg/3wk		1.94(-10.58,14.38)
IM TE 50-400 mg/1-2 wk		-1.57(-15.93,12.57)
IM TC 200 mg/2 wk		-13.12(-25.76,-0.50)
IM TC 200 mg/4 wk		-15.02(-27.02,-2.97)
IM TC 250 mg/2wk		-6.59(-18.64,5.51)
Durateston, IM, 250 mg/4wk		-14.65(-26.65,-2.55)
IM TU 1000 mg/12 wk	IM TU 1000 mg/10 wk	2.75(-3.39,8.87)
IM TE 100 mg/wk		3.82(-4.02,11.63)
IM TE 125 mg/wk		1.06(-10.55,12.59)
IM TE 150 mg/2wk		7.00(-3.13,17.12)
IM TE 200 mg/2wk		4.97(-2.38,12.33)
IM TE 250 mg/3wk		2.63(-5.20,10.43)
IM TE 300 mg/3wk		12.55(2.61,22.50)
IM TE 50-400 mg/1-2 wk		9.04(-3.15,21.15)
IM TC 200 mg/2 wk		-2.51(-12.86,7.88)
IM TC 200 mg/4 wk		-4.41(-13.89,5.12)
IM TC 250 mg/2wk		4.03(-5.67,13.61)
Durateston, IM, 250 mg/4wk		-4.03(-13.63,5.52)
IM TE 100 mg/wk	IM TU 1000 mg/12 wk	1.07(-4.91,7.00)
IM TE 125 mg/wk		-1.69(-12.18,8.70)
IM TE 150 mg/2wk		4.25(-4.40,13.04)
IM TE 200 mg/2wk		2.22(-3.10,7.50)
IM TE 250 mg/3wk		-0.12(-5.92,5.72)
IM TE 300 mg/3wk		9.80(1.20,18.32)
IM TE 50-400 mg/1-2 wk		6.29(-4.89,17.26)
IM TC 200 mg/2 wk		-5.26(-14.26,3.76)
IM TC 200 mg/4 wk		-7.16(-14.34,0.12)
IM TC 250 mg/2wk		1.28(-6.89,9.44)
Durateston, IM, 250 mg/4wk		-6.78(-14.19,0.56)
IM TE 125 mg/wk	IM TE 100 mg/wk	-2.76(-14.21,8.71)

IM TE 150 mg/2wk		3.19(-6.80,13.17)
IM TE 200 mg/2wk		1.15(-6.03,8.28)
IM TE 250 mg/3wk		-1.19(-8.76,6.47)
IM TE 300 mg/3wk		8.74(-1.14,18.58)
IM TE 50-400 mg/1-2 wk		5.22(-6.94,17.26)
IM TC 200 mg/2 wk		-6.32(-16.59,3.99)
IM TC 200 mg/4 wk		-8.22(-17.53,1.14)
IM TC 250 mg/2wk		0.21(-9.33,9.74)
Durateston, IM, 250 mg/4wk		-7.85(-17.40,1.61)
IM TE 150 mg/2wk	IM TE 125 mg/wk	5.95(-7.16,19.13)
IM TE 200 mg/2wk		3.91(-7.29,15.04)
IM TE 250 mg/3wk		1.57(-9.82,13.12)
IM TE 300 mg/3wk		11.50(-1.54,24.55)
IM TE 50-400 mg/1-2 wk		7.98(-6.80,22.76)
IM TC 200 mg/2 wk		-3.56(-16.94,9.75)
IM TC 200 mg/4 wk		-5.47(-18.14,7.27)
IM TC 250 mg/2wk		2.97(-9.79,15.85)
Durateston, IM, 250 mg/4wk		-5.09(-17.80,7.77)
IM TE 200 mg/2wk	IM TE 150 mg/2wk	-2.04(-11.66,7.57)
IM TE 250 mg/3wk		-4.38(-14.31,5.56)
IM TE 300 mg/3wk		5.55(-6.15,17.34)
IM TE 50-400 mg/1-2 wk		2.04(-11.74,15.72)
IM TC 200 mg/2 wk		-9.51(-21.66,2.54)
IM TC 200 mg/4 wk		-11.41(-22.70,0.00)
IM TC 250 mg/2wk		-2.98(-14.42,8.45)
Durateston, IM, 250 mg/4wk		-11.04(-22.52,0.42)
IM TE 250 mg/3wk	IM TE 200 mg/2wk	-2.34(-9.48,4.87)
IM TE 300 mg/3wk		7.59(-1.89,17.04)
IM TE 50-400 mg/1-2 wk		4.07(-7.82,15.86)
IM TC 200 mg/2 wk		-7.47(-17.31,2.38)
IM TC 200 mg/4 wk		-9.37(-18.42,-0.35)
IM TC 250 mg/2wk		-0.94(-9.99,8.19)
Durateston, IM, 250 mg/4wk		-9.00(-18.14,0.03)
IM TE 300 mg/3wk	IM TE 250 mg/3wk	9.93(0.08,19.73)
IM TE 50-400 mg/1-2 wk		6.41(-5.72,18.40)
IM TC 200 mg/2 wk		-5.13(-15.34,5.05)
IM TC 200 mg/4 wk		-7.04(-16.28,2.31)
IM TC 250 mg/2wk		1.40(-8.03,10.77)
Durateston, IM, 250 mg/4wk		-6.66(-16.10,2.75)
IM TE 50-400 mg/1-2 wk	IM TE 300 mg/3wk	-3.51(-17.11,9.98)
IM TC 200 mg/2 wk		-15.06(-26.99,-3.12)
IM TC 200 mg/4 wk		-16.96(-28.18,-5.70)

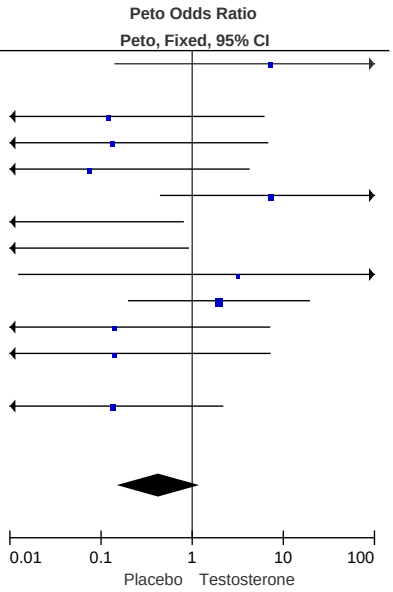
IM TC 250 mg/2wk		-8.53(-19.81,2.78)
Durateston, IM, 250 mg/4wk		-16.59(-27.91,-5.27)
IM TC 200 mg/2 wk	IM TE 50-400 mg/1-2 wk	-11.55(-25.33,2.34)
IM TC 200 mg/4 wk		-13.45(-26.71,-0.08)
IM TC 250 mg/2wk		-5.01(-18.35,8.45)
Durateston, IM, 250 mg/4wk		-13.07(-26.35,0.29)
IM TC 200 mg/4 wk	IM TC 200 mg/2 wk	-1.90(-13.46,9.66)
IM TC 250 mg/2wk		6.53(-5.16,18.17)
Durateston, IM, 250 mg/4wk		-1.53(-13.18,10.07)
IM TC 250 mg/2wk	IM TC 200 mg/4 wk	8.44(-2.47,19.30)
Durateston, IM, 250 mg/4wk		0.37(-6.93,7.65)
Durateston, IM, 250 mg/4wk	IM TC 250 mg/2wk	-8.06(-19.21,2.97)

eFigure 6: Odds of myocardial infarction associated with the use of any testosterone v. placebo

Study or Subgroup	Testosterone Events	Testosterone Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Year
Basaria 2015, p. 580	1	155	0	151	6.8%	7.20 [0.14, 363.02]	
Amory 2004	0	24	0	24		Not estimable	2004
Kenny 2010	0	69	1	62	6.8%	0.12 [0.00, 6.13]	2010
Srinivas-Shankar 2010	0	138	1	136	6.8%	0.13 [0.00, 6.72]	2010
Kalinchenko 2010	0	113	1	71	6.5%	0.07 [0.00, 4.20]	2010
Basaria 2010	2	106	0	103	13.6%	7.25 [0.45, 116.75]	2010
Aversa 2010 p. 776	0	42	1	10	4.2%	0.01 [0.00, 0.80]	2010
Aversa 2010 p. 3495	0	40	1	10	4.4%	0.01 [0.00, 0.90]	2010
Kaufman 2011	1	234	0	40	3.4%	3.23 [0.01, 830.32]	2011
Ho 2011	2	60	1	60	20.1%	1.97 [0.20, 19.31]	2011
Jones 2011	0	108	1	112	6.8%	0.14 [0.00, 7.07]	2011
Gianatti 2014	0	43	1	45	6.8%	0.14 [0.00, 7.14]	2014
Paduch 2015	0	35	0	39		Not estimable	2015
Snyder 2016	0	394	2	394	13.6%	0.13 [0.01, 2.16]	2016
Brock 2016	0	354	0	356		Not estimable	2016
Total (95% CI)		**1915**		**1613**	**100.0%**	**0.43 [0.15, 1.19]**	
Total events	6		10				

Heterogeneity: Chi² = 16.64, df = 11 (P = 0.12); I² = 34%

Test for overall effect: Z = 1.62 (P = 0.10)

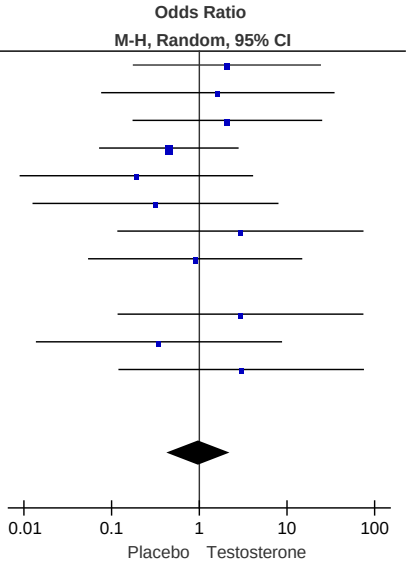


eFigure 7: Odds of prostate cancer associated with the use of any testosterone v. placebo

Study or Subgroup	Testosterone Events	Testosterone Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Dobs 1999	2	33	1	33	11.4%	2.06 [0.18, 23.94]	1999
Steidle 2003	2	307	0	99	7.4%	1.63 [0.08, 34.21]	2003
Amory 2004	2	24	1	24	11.2%	2.09 [0.18, 24.73]	2004
Marks 2006	2	22	4	22	20.8%	0.45 [0.07, 2.76]	2006
Emmelot-Vonk 2009	0	120	2	117	7.4%	0.19 [0.01, 4.04]	2009
Srinivas-Shankar 2010	0	138	1	132	6.6%	0.32 [0.01, 7.84]	2010
Basaria 2010	1	106	0	103	6.6%	2.94 [0.12, 73.08]	2010
Kenny 2010	1	69	1	62	8.8%	0.90 [0.05, 14.65]	2010
Shigehara 2011	0	26	0	26		Not estimable	2011
Behre 2012	1	183	0	179	6.6%	2.95 [0.12, 72.91]	2012
Hackett 2013	0	97	1	102	6.6%	0.35 [0.01, 8.62]	2013
Snyder 2016	1	394	0	394	6.7%	3.01 [0.12, 74.05]	2016
Brock 2016	0	358	0	356		Not estimable	2016
Total (95% CI)		**1877**		**1649**	**100.0%**	**0.97 [0.43, 2.23]**	
Total events	12		11				

Heterogeneity: Tau² = 0.00; Chi² = 4.89, df = 10 (P = 0.90); I² = 0%

Test for overall effect: Z = 0.06 (P = 0.95)

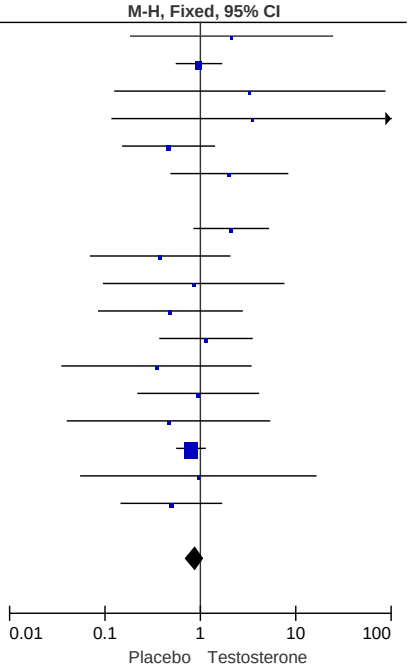


eFigure 8: Odds of serious adverse events: any testosterone v. placebo

Study or Subgroup	Testosterone Events	Testosterone Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Ng Tang Fui 2016	2	49	1	51	0.6%	2.13 [0.19, 24.25]	
Basaria 2015, p. 580	33	155	33	151	16.9%	0.97 [0.56, 1.67]	
Bhasin 1998	1	20	0	21	0.3%	3.31 [0.13, 86.06]	1998
Simon 2001	1	6	0	6	0.3%	3.55 [0.12, 105.82]	2001
Emmelot-Vonk 2009	5	120	10	117	6.2%	0.47 [0.15, 1.41]	2009
Srinivas-Shankar 2010	6	138	3	136	1.9%	2.02 [0.49, 8.23]	2010
Aversa 2010 p. 776	0	42	0	10		Not estimable	2010
Basaria 2010	16	106	8	103	4.4%	2.11 [0.86, 5.17]	2010
Ho 2011	2	60	5	60	3.1%	0.38 [0.07, 2.04]	2011
Kaufman 2011	5	234	1	40	1.1%	0.85 [0.10, 7.49]	2011
Spitzer 2012	2	70	4	70	2.5%	0.49 [0.09, 2.74]	2012
Behre 2012	7	183	6	179	3.8%	1.15 [0.38, 3.48]	2012
Hackett 2013	1	97	3	103	1.9%	0.35 [0.04, 3.40]	2013
Gianatti 2014	4	45	4	43	2.4%	0.95 [0.22, 4.07]	2014
Basaria 2015, p. 280	1	43	2	41	1.3%	0.46 [0.04, 5.33]	2015
Snyder 2016	77	394	92	394	47.7%	0.80 [0.57, 1.12]	2016
Magnussen 2016	1	22	1	21	0.6%	0.95 [0.06, 16.28]	2016
Brock 2016	4	354	8	356	5.1%	0.50 [0.15, 1.67]	2016
Total (95% CI)		**2138**		**1902**	**100.0%**	**0.88 [0.70, 1.11]**	
Total events	168		181				

Heterogeneity: Chi² = 11.90, df = 16 (P = 0.75); I² = 0%

Test for overall effect: Z = 1.11 (P = 0.27)



eTable 11: Odds of serious adverse events associated with individual testosterone products – Bayesian network meta-analysis

	Odds ratio (95% credible interval)*							
	Placebo	**Gel 1%, 50 mg/d**	**Gel 1%, 75 mg/d**	**Gel 1%, 100 mg/d**	**Gel 1.62%, 40.5 mg/d**	**Solution 2%, 60 mg/d**	**Oral TU, 160 mg/d**	**IM TU, 1000 mg/12 wk**
Gel 1%, 50 mg/d	0.91 (0.46,2.10)	—						
Gel 1%, 75 mg/d	0.98 (0.25,3.55)	1.08 (0.21,4.42)	—					
Gel 1%, 100 mg/d	1.41 (0.39,4.06)	1.54 (0.31,5.25)	1.45 (0.23,7.53)	—				
Gel 1.62%, 40.5 mg/d	1.19 (0.11,40.82)	1.30 (0.10,48.76)	1.24 (0.09,51.17)	0.89 (0.07,35.34)	—			
Solution 2%, 60mg/d	0.47 (0.08,2.53)	0.51 (0.07,3.07)	0.48 (0.06,4.08)	0.34 (0.04,2.88)	0.38 (0.01,7.32)	—		
Oral TU 160 mg/d	0.45 (0.08,2.17)	0.49 (0.07,2.67)	0.46 (0.05,3.60)	0.32 (0.05,2.51)	0.36 (0.01,6.21)	0.94 (0.09,10.03)	—	
IM TU,1000 mg/12 wk	0.68 (0.23,1.94)	0.74 (0.18,2.56)	0.69 (0.13,3.70)	0.48 (0.11,2.55)	0.56 (0.01,7.68)	1.43 (0.20,11.31)	1.50 (0.23,10.76)	—

Note: IM = intramuscular injection, TU = testosterone undecanoate.

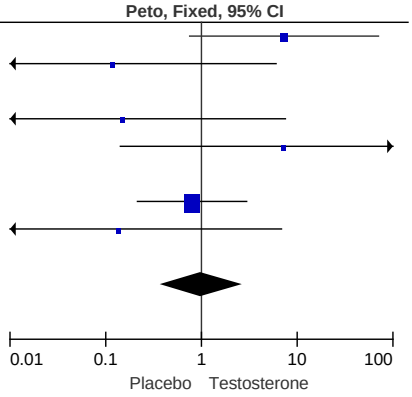
*Random effects model. Significant changes are indicated by use of bold and colour (green indicates that the row treatment treatement is significantly better than the column treatment, while red indicates that the row treatment is significantly worse than the column treatment). White indicates no significant difference between treatments. An additional 4 RCTs (Aversa 2010; Schubert 2004; Bhasin 1998; Simon 2001) could not be included in the network because they reported zero events in ≥ treatment groups.

eFigure 9: Odds of stroke associated with the use of any testosterone v. placebo

Study or Subgroup	Testosterone Events	Testosterone Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Year
Basaria 2015, p. 580	3	155	0	151	18.8%	7.30 [0.75, 70.67]	
Sih 1997	0	17	1	15	6.3%	0.12 [0.00, 6.02]	1997
Amory 2004	0	24	0	24		Not estimable	2004
Brockenbrough 2006	0	19	1	21	6.3%	0.15 [0.00, 7.54]	2006
Basaria 2010	1	106	0	103	6.3%	7.18 [0.14, 362.14]	2010
Paduch 2015	0	35	0	39		Not estimable	2015
Snyder 2016	4	394	5	394	56.1%	0.80 [0.21, 2.97]	2016
Brock 2016	0	354	1	356	6.3%	0.14 [0.00, 6.86]	2016
Total (95% CI)		**1104**		**1103**	**100.0%**	**0.99 [0.37, 2.65]**	
Total events	8		8				

Heterogeneity: Chi² = 7.06, df = 5 (P = 0.22); I² = 29%

Test for overall effect: Z = 0.02 (P = 0.99)

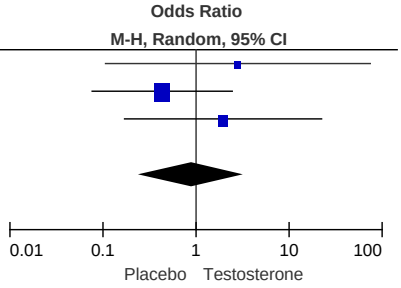


eFigure 10: Odds of heart disease associated with the use of any testosterone v. placebo

Study or Subgroup	Testosterone Events	Testosterone Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Sih 1997	1	17	0	15	15.7%	2.82 [0.11, 74.51]	1997
Kenny 2010	2	69	4	62	56.0%	0.43 [0.08, 2.45]	2010
Gianatti 2014	2	45	1	43	28.3%	1.95 [0.17, 22.36]	2014
Total (95% CI)		**131**		**120**	**100.0%**	**0.89 [0.24, 3.26]**	
Total events	5		5				

Heterogeneity: Tau² = 0.00; Chi² = 1.54, df = 2 (P = 0.46); I² = 0%

Test for overall effect: Z = 0.18 (P = 0.86)

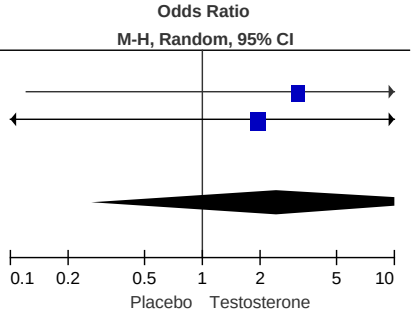


eFigure 11: Odds of erythrocytosis associated with the use of any testosterone v. placebo

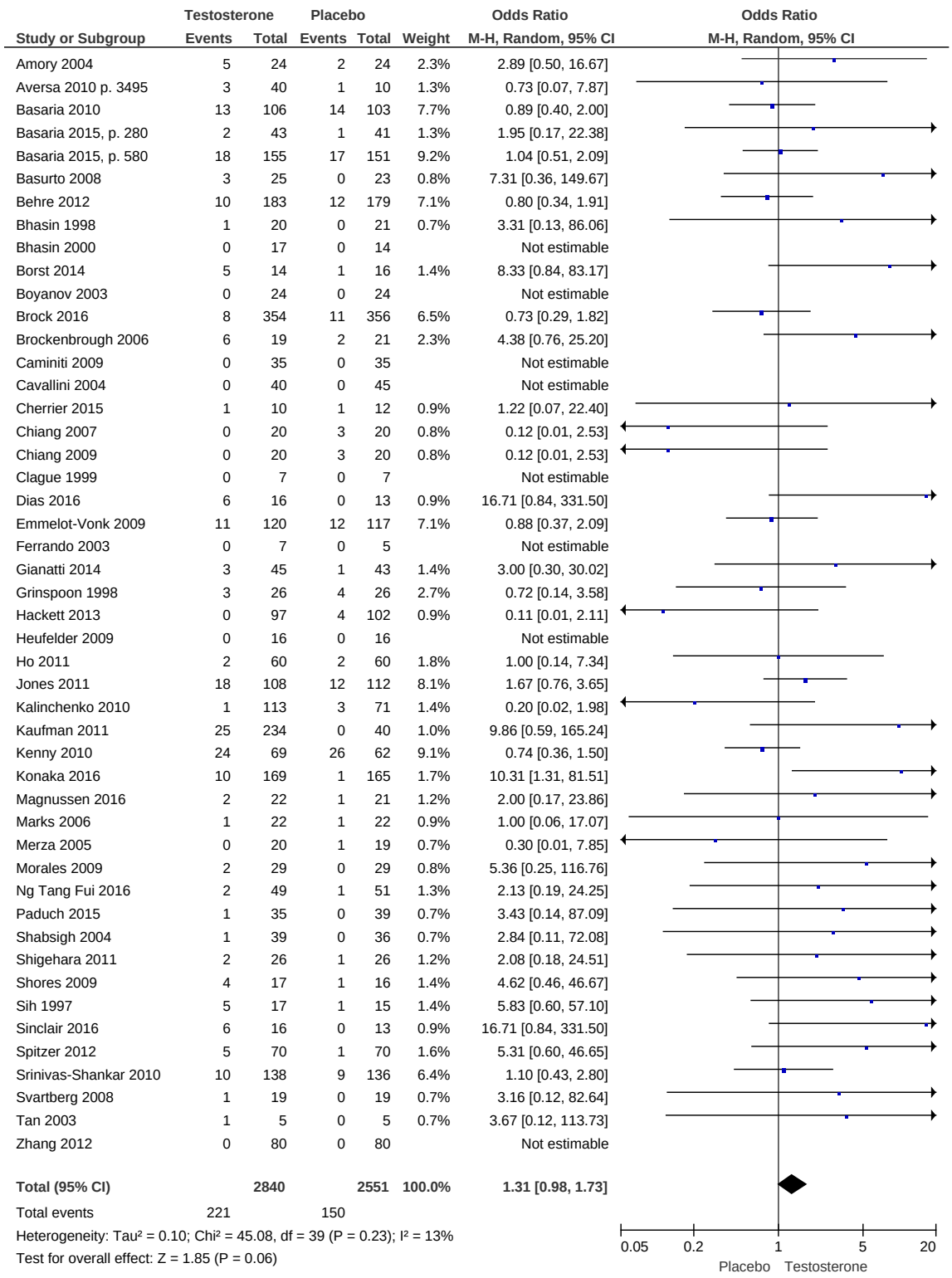
Study or Subgroup	Testosterone Events	Testosterone Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Tan 2003	0	5	0	5		Not estimable	2003
Marks 2006	1	22	0	22	46.6%	3.14 [0.12, 81.35]	2006
Aversa 2010 p. 3495	3	40	0	10	53.4%	1.96 [0.09, 41.02]	2010
Basaria 2015, p. 280	0	43	0	41		Not estimable	2015
Total (95% CI)		**110**		**78**	**100.0%**	**2.44 [0.26, 22.53]**	
Total events	4		0				

Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.84); I² = 0%

Test for overall effect: Z = 0.79 (P = 0.43)



eFigure 12: Odds of withdrawals due to adverse events associated with the use of any testosterone v. placebo



eTable 12: Odds of withdrawals due to adverse events associated with individual testosterone products – Bayesian network meta-analysis

	Odds ratio (95% credible interval)*																
	Placebo	Patch, 5 mg/d	Gel 1%, 5 mg/d	Gel 1%, 50 mg/d	Gel 1%, 75 mg/d	Gel 1%, 100 mg/d	Gel 2%, 60 mg/d	Solution 2%, 60 mg/d	Oral TU 160 mg/d	IM TU, 1000 mg/10 wk	IM TU, 1000 mg/12 wk	IM TE, 125 mg/ wk	IM TE, 150 mg/ 2 wk	IM TE, 200 mg/ 2 wk	IM TE, 250 mg/ 4 wk	IM TE, 300 mg/ 3 wk	IM TC, 200 mg/ 2 wk
Patch, 5 mg/d	**6.82 (1.66, 32.14)**	—															
Gel 1%, 5 mg/d	0.76 (0.27, 2.14)	**0.11 (0.02, 0.63)**	—														
Gel 1%, 50 mg/d	1.45 (0.77, 3.00)	**0.21 (0.05, 0.86)**	1.91 (0.59, 6.89)	—													
Gel 1%, 75 mg/d	1.30 (0.55, 3.57)	0.19 (0.03, 1.07)	1.71 (0.46, 7.48)	0.90 (0.29, 2.85)	—												
Gel 1%, 100 mg/d	1.03 (0.45, 2.40)	**0.15 (0.03, 0.64)**	1.36 (0.37, 5.19)	0.71 (0.25, 1.90)	0.79 (0.22, 2.61)	—											
Solution 2%, 60 mg/d	1.64 (0.57, 4.95)	0.24 (0.04, 1.42)	2.18 (0.50, 9.67)	1.14 (0.30, 3.98)	1.26 (0.28, 4.94)	1.60 (0.40, 6.12)	—										
Gel 2%, 60 mg/d	0.73 (0.21, 2.37)	**0.11 (0.01, 0.67)**	0.96 (0.19, 4.68)	0.50 (0.12, 1.88)	0.56 (0.11, 2.35)	0.70 (0.16, 2.93)	0.44 (0.08, 2.23)	—									
Oral TU 160 mg/d	0.87 (0.28, 2.77)	**0.13 (0.02, 0.80)**	1.15 (0.25, 5.43)	0.60 (0.15, 2.23)	0.67 (0.14, 2.77)	0.84 (0.20, 3.54)	0.53 (0.11, 2.61)	1.20 (0.23, 6.61)	—								
IM TU, 1000 mg/10 wk	2.14 (0.18, 33.83)	0.31 (0.02, 7.21)	2.85 (0.20, 53.28)	1.48 (0.11, 24.89)	1.64 (0.12, 28.93)	2.08 (0.16, 37.59)	1.29 (0.09, 25.16)	2.95 (0.20, 59.09)	2.47 (0.17, 49.97)	—							
IM TU, 1000 mg/12 wk	0.52 (0.21, 1.26)	**0.08 (0.01, 0.40)**	0.69 (0.17, 2.72)	0.36 (0.11, 1.05)	0.40 (0.10, 1.36)	0.50 (0.15, 1.68)	0.31 (0.08, 1.28)	0.72 (0.16, 3.21)	0.59 (0.14, 2.52)	0.24 (0.01, 3.42)	—						
IM TE, 125 mg/ wk	7.95 (0.97, 105.20)	1.20 (0.09, 22.88)	**10.65 (1.03, 166.10)**	5.47 (0.60, 77.02)	6.08 (0.60, 90.45)	7.72 (0.80, 115.20)	4.89 (0.44, 78.95)	**11.35 (1.01, 179.70)**	9.32 (0.83, 152.60)	3.88 (0.11, 140.30)	**15.62 (1.59, 244.70)**	—					

Supplemental Online Content: Elliott et al. Testosterone therapy in hypogonadal men: a systematic review and network meta-analysis.

IM TE, 150 mg/ 2 wk	1.01 (0.04, 22.84)	0.15 (0.00, 4.20)	1.34 (0.05, 34.59)	0.70 (0.03, 16.50)	0.77 (0.03, 18.63)	0.97 (0.04, 24.53)	0.62 (0.02, 17.03)	1.39 (0.05, 39.21)	1.16 (0.05, 33.97)	0.46 (0.01, 25.13)	1.95 (0.08, 49.97)	0.12 (0.00, 4.99)	—			
IM TE, 200 mg/ 2 wk	2.83 (0.49, 21.73)	0.42 (0.04, 4.94)	3.78 (0.49, 36.13)	1.96 (0.29, 16.21)	2.17 (0.28, 19.79)	2.73 (0.39, 24.40)	1.73 (0.22, 17.02)	3.93 (0.48, 41.61)	3.26 (0.40, 32.63)	1.38 (0.05, 28.67)	5.50 (0.74, 50.37)	0.35 (0.02, 6.55)	2.92 (0.08, 107.60)	—		
IM TE, 250 mg/ 4 wk	5.92 (1.43, 36.28)	0.89 (0.10, 8.37)	**8.05 (1.33, 61.53)**	4.12 (0.82, 27.64)	4.61 (0.77, 32.91)	**5.81 (1.08, 41.07)**	3.66 (0.59, 29.86)	**8.31 (1.27, 72.32)**	**6.95 (1.08, 57.31)**	2.88 (0.11, 57.41)	11.75 (2.13, 84.99)	0.75 (0.04, 11.64)	6.10 (0.20, 202.50)	2.15 (0.18, 25.19)	—	
IM TE, 300 mg/ 3 wk	0.72 (0.11, 4.20)	**0.10 (0.01, 0.99)**	0.93 (0.11, 7.44)	0.49 (0.06, 3.19)	0.54 (0.07, 3.89)	0.69 (0.09, 4.94)	0.43 (0.05, 3.45)	0.98 (0.10, 8.51)	0.82 (0.09, 7.04)	0.33 (0.01, 6.96)	1.38 (0.18, 10.17)	0.09 (0.00, 1.40)	0.71 (0.02, 23.91)	0.24 (0.02, 2.99)	0.12 (0.01, 1.18)	—
IM TC, 200 mg/ 2 wk	5.77 (0.72, 76.47)	0.85 (0.06, 15.32)	7.73 (0.72, 116.20)	3.98 (0.43, 54.25)	4.37 (0.43, 64.41)	5.53 (0.60, 78.93)	3.52 (0.33, 54.96)	8.03 (0.71, 131.40)	6.60 (0.62, 104.30)	2.73 (0.09, 84.03)	**11.06 (1.15, 170.30)**	0.72 (0.03, 19.57)	5.92 (0.14, 282.40)	2.07 (0.10, 43.57)	0.95 (0.06, 17.27)	8.60 (0.51, 180.50)	—

Note: IM = intramuscular injection, TC = testosterone cypionate, TE = testosterone enanthate, TU = testosterone undecanoate.

*Random-effects model. Significant changes are indicated by use of bold and colour (green indicates that the row treatment treatement is significantly better than the column treatment, which red indicates that the row treatment is signigicantly worse than the column treatment). White indicates no significant difference between treatments. An additional 23 studies (Basurto 2008, Bhasin 1998 (p. 140), Bhasin 1998 (p. 3155), Boyanov 2003, Caminiti 2009, Cavallini 2004, Chiang 2007, Chiang 2009, Clague 1999, Dobs 1999, Ferrando 2003, Hackett 2013, Heufelder 2009, Kaufman 2011, Merza 2005, Morales 2009, Schubert 2004, Shabsigh 2004, Svartberg 2008, Tan 2003, Zhang 2012, Dias 2016, Paduch 2015) were removed from the network meta-analysis because zero events were reported in one or both groups.

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eTable 13: Summary of harms outcomes reported in non-randomized studies

Author, year	Population	Treatment (no. in group)	Outcome	Comments
Retrospective cohort				
Cheetham 2017	≥ 40 yr with documented androgen deficiency	• Ever TRT (8,808) • Never TRT (35,527) Mean follow-up: 4.4 years (median 3.4 years, IQR, 1.7-6.5 years)	• Stroke: AHR 0.64 (95% CI 0.52, 0.80) • Acute MI: AHR 0.74 (95% CI 0.63, 0.86) • CVD: AHR 0.76 (95% CI 0.61, 0.93)	Entry into cohort was based on filling a prescription for TRT (patch 13.6%, gel 34.7%, injectable 51.6%).
Layton 2015	New users of TRT	• Gel (109,810) • Injection (103,555) • Patch (9,255) Mean treatment duration between 96 days (patch) and 122 days (injection)	Injection v. gel • MI: AHR 1.64 (95% CI 0.57, 4.69) • Stroke: AHR 1.28 (0.27, 6.02)	No significant difference in MI or stroke between injection and gel users. No data available for patch v. injection or gel users.
Pastuszak 2015	New TRT users or had been off TRT for ≥ 3 or mo	• Gel (1% 50–100mg/d or 1.62% 20.25–80.1 mg/d) (47) • IM TE or TC, 100–200mg/wk (57) • Pellets (75mg/3–6 mo) (74) Duration: 36 mo	• Erythrocytosis: Gel: 12.8% of patients Injection: T 66.7% Pellets: 35.1% • Prostate cancer: 1 case of prostate cancer diagnosed in pellet group. No new cases of prostate cancer among men with previous prostate cancer.	Erythrocytosis defined as hematocrit ≥50%; Erythrocytosis occurred significantly earlier in the injection group (10.5±9.1 mo) compared with the gel (14.0±12.6 mo) or pellet (16.4 ±10.7mo) groups.
Ramasamy 2015	≥ 65 yr and ≥3 hypogonadal symptoms	• TRT, dose NR (153) • No TRT, dose NR (64) Duration: Median follow-up 3.8 (TRT) v. 3.4 yr (TRT)	•MI: 1 event in TRT group v. 0 in no TRT group • Stroke: 2 events in TRT v. 1 in no TRT group	All events (except 1 death which took place after 6 months of follow-up) occurred after 2 or more years.
Vigen 2013	Men who underwent coronary angiography	• TRT, dose NR (1223) • No TRT (7486) Mean follow-up: 840 d	• Cardiovascular events†: AHR 1.29, 95% CI 1.04 to 1.58	Entry into cohort was based on filling a prescription for TRT (patch, gel, or injectable). Data reported as TRT v. no TRT. Length of follow-up differed by group.
Shores 2012	> 40 yr treated at a VA medical center, inpatient or outpatient	• No TRT (633) • TRT (398) Duration: 20.2 mo	• Prostate cancer: No treatment: 13/633 men; TRT: 7/398 men	Data reported as TRT v. no TRT. TRTs included injectable, patch, or gel.
Rhoden 2006	Negative prostate biopsy prior to starting TRT	• IM testosterone, dose and type NR (33) • Gel 1%, dose NR (25) Duration: 12 mo	• Prostate cancer: 1 case in the IM group	
Guay 2000	Men with ED and primary or secondary hypogonadism	• IM TE, 200–300 mg/2–3 wk (25) • Patch, 5 mg/d (16)	• Prostate cancer: 3 cases (NR to which treatment group the patients belonged)	

		Duration: 2–3 mo		
Prospective cohort				
Debruyne 2017	≥18 yr with a diagnosis of hypogonadism	• TRT, dose NR (750) • No TRT (249) Duration: 36 mo (23,900 person-mo)	• Prostate cancer: incidence rate ratio 0.52 (95% CI 0.22 to 1.26)	68% of TRT users recieved topical gels, 31% injectables, and 2% oral products
Traish 2017	Symptoms of hypogonadism	• TU, 1000mg/12wk (360) • No TRT (296) Median follow-up: 7 yr	• CVD: 0 in TU group v. 19 in no TRT group • Nonfatal MI: 0 in TU group v. 26 in no TRT group • Nonfatal stroke: 0 in TU group v. 30 in no TRT group • Prostate cancer: 7 in TU group v. 12 in no TRT group	CVD in no TRT group attributed to MI (5), stroke (4), heart failure (7), thromboembolism (2), lung embolism (1), and pneumonia and lung failure (1)
Yassin 2017	Treated or untreated hypogonadal men	• TRT, dose NR (42) • No treatment (162) Duration: 6 yr	• Prostate cancer: 7 (16.7%) in TRT group vs. 84 (51.9%) in untreated group	Data reported as a positive biopsy for prostate cancer; lower severity of prostate cancer in terms of staging and grading in the TRT group than in the untreated group
Jung 2016	Symptoms of hypogonadism	• TU, 1000 mg/3 mo + lifestyle modification (54) • Lifestyle modification (52) Treatment duration: 8 mo	• Prostate cancer: 0 in both groups • MI: 0 in both groups • Stroke: 0 in both groups	Prospective, controlled study
Francomano 2014	Severely obese men (mean BMI 42) with ≥ 2 symptoms of hypogonadism	• DPE (12) • DPE + IM TU, 1000 mg/12 wk (12) Duration: 54 wk + 24 wk observational period following withdrawal of treatment	• WAE: zero in both groups • SAE: zero in both groups	
Aydogdu 2013	IHH	• Sustanon, 250 mg/3wk (28) • Gel 1%, 50 mg/d (24) Duration: 24 wk	• SAE: zero in all groups	
Blick 2013	HIV/AIDS	• Androgel 1%, gel, 50 mg/d (92) • Testim 1%, gel, 50 mg/d (75) Duration: 12 mo	• Erythrocytosis: zero in both groups • Prostate cancer: zero in both groups • WAE: zero in both groups	
Aversa 2012	Middle-aged men with LOH and MetS	• No treatment (20) • IM TU, 12 wk (40) Duration: 36 mo	• MI: 1 in control group • Erythrocytosis: 4 in TU group	
6Wang 2004	19–68 yr	• Gel 1%, 50 mg/d (NR) • Gel 1%, 75 mg/d (NR) • Gel 1%, 100 mg/d (NR) Total: 163 men Duration: 36 mo‡	•Prostate cancer: 1 in 75 mg/d group, 2 in 100 mg/d group • Skin reactions: 12 men	

Hajjar 1997	Elderly men	• No treatment (27) • IM TE or TC 200mg/2-3 wk (45) Duration: at least 2 yr	• Myocardial infarction: 1 in TRT group • Stroke: No treatment: 1/23; TRT: 1/26 • Diabetes: No treatment: 0/23; TRT: 1/26 • Erythrocytosis¶: No treatment: 0/27; TRT: 11/45	Safety outcomes were reported based on a subset of people assigned to each group

Note: AHR = adjusted hazard ratio, DPE = diet plus exercise, ED = erectile dysfunction, IHH = idiopathic hypogonadotropic hypogonadism, IM = intramuscular injection, LOH = late-onset hypogonadism, MetS = metabolic syndrome, MI = myocardial infarction, NR = not reported, SAE = serious adverse event, TC = testosterone cypionate, TE = testosterone enanthate, TU = testosterone undecanoate, TRT = testosterone replacement therapy, T = testosterone, VA = Veterans Affairs, WAE = withdrawal due to adverse events.

†Composite outcome of all-cause mortality, myocardial infarction, and ischemic stroke. MI, stroke and CV death were also reported separately; however the length of observation time differed between groups.

‡ This study was completed after an initial 6-month randomized study for an additional 36 months; participants had a total of 42 months of gel exposure.

¶Reported as polycythemia for the treatment group. Zero count inferred for the control group.

PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	**p. 1**
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	**p. 3**
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known*, including mention of why a network meta-analysis has been conducted.*	**p. 6**
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	**p. 6**
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	**p. 2,5,6**
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*	**p. 6-7**
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify	**p. 7**

		additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Online supplement
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	**p. 7**
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	**p. 7**
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	**p. 8**
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	**p. 8-9**
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	**p. 7-8**
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	**p. 8-9**
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	**p. 8-9**
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	**p. 8-9**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	**p. 7-8**
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses;	**NA**

		• *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	
RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	**p. 10, Figure 1**
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	**Fig 3, supplement**
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	**Supplement (eAppendix 4)**
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	**Supplement (eTable 1,2)**
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	**Supplement (eTable 3,4)**
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	**Supplement**
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	**p. 9-13, supplement**
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	**p. 10, supplement (eAppendix 5)**
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	**p. 9, Supplement (eTable 3,4)**
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses*, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	**NA**

DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	**p. 13**
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	**p. 15**
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	**p. 15-16**
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	**p. 2**