Testosterone Replacement Therapy and the Risk of Venous Thromboembolism: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Henok Tadesse Ayele PhD,[1] Vanessa C. Brunetti MSc,[2] Christel Renoux MD PhD,[3] Vicky Tagalakis MD MSc,[4] and Kristian B. Filion PhD [5]

[1] Department of Epidemiology, Biostatistics, Occupational Health, McGill University; and Center for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, 3755 Cote Ste-Catherine, Montreal, Quebec, H3T 1E2, Canada; E-mail: henok.ayele@mail.mcgill.ca
[2] Department of Epidemiology, Biostatistics, Occupational Health, McGill University; and Center for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, 3755 Cote Ste-Catherine, Montreal, Quebec, H3T 1E2, Canada; E-mail: vanessa.brunetti@mail.mcgill.ca
[3] Department of Epidemiology, Biostatistics, Occupational Health and Department of Neurology and Neurosurgery, McGill University; and Center for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, 3755 Cote Ste-Catherine, Montreal, Quebec, H3T 1E2, McGill University, Montreal, Quebec, Canada. E-mail: christel.renoux@mcgill.ca
[4] Division of General Internal Medicine, Department of Medicine, Jewish General Hospital, McGill University; Department of Epidemiology, Biostatistics, Occupational Health, McGill University; and Center for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, 3755 Cote Ste-Catherine, Montreal, Quebec, H3T 1E2, Canada. E-mail: vicky.tagalakis@mcgill.ca
[5] Departments of Medicine and of Epidemiology, Biostatistics, Occupational Health, McGill University; and Center for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, 3755 Cote Ste-Catherine, Montreal, Quebec, H3T 1E2, Canada. E-mail: kristian.filion@mcgill.ca

The poster of this manuscript was presented at the 36th International Conference on Pharmacoepidemiology & Therapeutic Risk Management (ICPE 2020) on September 16th, 2020.

Body of Manuscript Word Count: 3793;
Abstract Word Count: 250

Corresponding author:
Kristian B. Filion, PhD
Associate Professor and William Dawson Scholar
Departments of Medicine and Epidemiology, Biostatistics, and Occupational Health
McGill University
3755 Cote Ste Catherine, Suite H410.1
Montreal, Quebec H3T 1E2 Canada

Phone: (514) 340-8222 x 28394
Fax: (514) 340-7564
Email: kristian.filion@mcgill.ca

ABSTRACT

Introduction: The cardiovascular safety of testosterone replacement therapy (TRT) is controversial. While several studies have investigated the association between TRT and the risk of arterial thrombosis, limited information is available regarding its risk of venous thromboembolism (VTE). We aimed to compare the risk of VTE in men randomized to TRT versus placebo or active-comparator in a systematic review.

Methods: We searched Medline, EMBASE, CINAHL, CENTRAL, and clinical trial registries to identify randomized controlled trials (RCTs) comparing TRT to placebo in men aged ≥18 years. We assessed study quality using the Cochrane Risk of Bias assessment tool and the overall quality of evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria. Data were pooled across RCTs using random-effects models.

Results: A total of 13 RCTs (n=5,050) were included in our meta-analysis. In all, 2,636 men were randomized to testosterone, and 2,414 men to placebo. Sample sizes ranged from 101 to 790 men, and TRT duration from 3 to 36 months. Five studies had a high risk of bias, largely driven by unclear randomization and outcome assessment. When data were pooled across RCTs, testosterone therapy was not associated with VTE compared with placebo (RR: 1.03, 95% CI: 0.49-2.14; I^2: 0%; low-quality evidence). Similar estimates were obtained for deep vein thrombosis and pulmonary embolism outcomes.

Conclusions: Our systematic review suggests that TRT is not associated with an increased risk of VTE. However, estimates were accompanied by a wide 95% CIs, and a clinically important increased risk cannot be ruled out.

Keywords: Testosterone, Venous Thromboembolism, Deep Vein Thrombosis, Pulmonary Embolism, Systematic Review, Meta-analysis.

INTRODUCTION

Testosterone replacement therapy (TRT) is prescribed for the management of low testosterone levels when hypogonadism[1] interferes with health or quality of life.[2,3] TRT use has increased 10-fold in North America[4] over the last 30 years, with a 12-fold increase in worldwide sales from $150 million to $1.8 billion during this period[4]. However, the use of TRT declined in recent years[5] following the publication of cardiovascular safety studies[6-9] and a subsequent safety warning surrounding this issue from the US Food and Drug Administration (FDA).[10] This warning was based on evidence that TRT can increase the risk of coronary artery dilation and potentially rupture an unstable plaque, resulting in myocardial infarction.[11]

While much attention has focused on TRT and the risk of arterial thrombosis, the effect of TRT on the risk of venous thromboembolism (VTE) remains poorly understood.[12] The US FDA[13] issued a labeling change in the product information of all approved TRT products regarding the risk of VTE. However, this change was based on limited evidence, consisting only of a case series of patients with VTE.[14-16] The lack of a reference group renders these data difficult to interpret. Moreover, the FDA positional statement on the benefits and safety of TRT in older men stressed the lack of conclusive data for this potential adverse drug effect.[10]

There exists both a strong biological rationale and emerging evidence that supports a potential association between TRT and VTE. TRT is hypothesized to interact with previously undiagnosed thrombophilia-hypofibrinolysis, leading to VTE.[17] In addition, several animal[18,19] and human[20,21] studies support the thrombogenic potential of TRT.[15,22,23] A number of randomized controlled trials (RCT) reported VTE as an adverse event of TRT; however, these trials were individually underpowered to examine this safety endpoint, resulting in imprecise estimates. Three previous observational studies have examined this association, reporting heterogeneous findings.[23-25] The association has also been examined in three previous systematic

reviews, which reported a disparate risk of VTE in men treated with TRT.[12,26,27] However, these previous systematic reviews had several important limitations, including the exclusion of potentially relevant studies. Consequently, there remains a need to synthesize the totality of the evidence regarding the risk of VTE with TRT. The objective of this systematic review and meta-analysis of RCTs was therefore to determine if TRT, compared with placebo or an active comparator, is associated with the risk of VTE among men ≥ 18 years.

METHODS

The protocol for this study was written following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 checklist (Appendix 1),[28] and the study is reported according to the PRISMA guidelines (Appendix 2).[29] The study involved aggregate, publicly available data and thus did not require research ethics approval.

Search Strategy

We systematically searched Medline (via Ovid; start date: 1946), Excerpta Medica dataBASE (EMBASE; start date: 1947), Cumulative Index of Nursing and Allied Health (CINAHL; start date: 1937), and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception to December 18th, 2019 for RCTs of TRT that reported VTE as an outcome, with the search strategy tailored to each database. The search was restricted to RCTs in Medline using the 2005 version of the Centre for Reviews and Dissemination/Cochrane Highly Sensitive Search Strategy filter.[30] In addition, ClinicalTrials.gov (www.clinicaltrials.gov) was searched for completed but still unpublished RCTs. Our database search was supplemented by a search of the World Health Organization trial registry and by a manual search of bibliographies of identified studies. Moreover, we used forward and backward citation searching with Scopus, and we searched the European Medical Agency (EMA) and FDA registries for unpublished trials on the safety of TRT. Finally, we reviewed the first 10 pages of Google Scholar for additional studies.

The search strategy was developed in collaboration with an experienced medical librarian. The construction of our search strategy was driven by two components of the Population, Intervention, Comparison, Outcome, and Time (PICOT) formatted research question: TRT (intervention) and VTE (outcome). VTE-related events were defined as anything

reported as such by the authors, that is, events reported as hepatic vein thrombosis, portal thrombosis, splanchnic venous thrombosis, pulmonary embolism or other venous thrombosis events. Ho et.al suggested that the use of a search strategy based on 2 elements of the PICOT question can identify a large number of relevant studies compared to 4 elements search.[31] Since many trials focused their safety assessment on CVD rather than VTE, we included search terms for CVD to identify trials that reported VTE as a secondary outcome or a serious adverse event. To restrict our search to RCTs conducted in humans, we added the MEDLINE Cochrane RCT filter as the third concept in our search strategy.[30] The Medline search is reproduced in full in Appendix 3.

Eligibility and Study Selection

RCTs that compared any commercially available TRT formulation to either placebo or an active comparator consisting of any androgenic medication (e.g., growth hormones, gonadotropin-releasing hormone antagonists), included a minimum of 50 participants in each group, and reported the risk of VTE by study arm were included in our systematic review. We included RCTs conducted in men aged 18 years or older. We excluded studies of women or children (<18 years) because they have different hormone levels than adult men.[32] We further excluded uncontrolled trials, observational studies, previous reviews and meta-analyses, case reports and case series, letters to the editor, editorials, and commentaries. We also excluded conference abstracts as the results of such studies are often not final, and abstracts contain insufficient information to adequately assess study quality. Finally, we excluded trials published in a language other than English or French.

Following the removal of duplicates, two independent reviewers (HTA and VCB) screened the titles and abstracts of publications identified by our electronic search. Any

publication deemed potentially relevant by either reviewer was carried forward to the full-text review. Discrepancies during the full-text review were resolved by consensus between two independent reviewers (HTA and VCB).

Data Extraction

We used an electronic form to extract data from the included studies (Appendix 4). Data extracted included: 1) study characteristics: authors' names, journal, year of publication, sample size (total and by groups), intervention definition, duration of follow-up, duration of TRT, route of TRT administration, and outcome definition; 2) baseline demographic and clinical characteristics: age, indication for TRT, TRT dose, and pre-existing comorbidities; 3) Count data, effect estimates, and corresponding 95% confidence intervals (CI) for VTE as well as deep vein thrombosis (DVT) and pulmonary embolism (PE); and 4) study quality, as defined by the Cochrane risk of bias tool (described below). Two independent reviewers (HTA and VCB) extracted relevant information, and disagreements were resolved by consensus. The authors were contacted by email to identify missing information on VTE outcomes, particularly for studies identified in the grey literature. At least two email attempts were made for each corresponding author.

Quality Assessment

Two authors (HTA and VCB) independently assessed study quality using the Cochrane Risk of Bias assessment tool version 2.0,[33] with discrepancies resolved by consensus. We also assessed funding sources as a potential source of bias; a trial was considered partially or completely supported by industry when declared by the authors or when at least one author was an employee of a pharmaceutical company, an approach used previously.[34] We assessed the

overall quality of evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) assessment criteria.[35]

Statistical Analyses

The primary outcome measure was the cumulative incidence ratio for VTE among participants randomized to TRT versus placebo or an active comparator, which we estimated using reported count data. Trials with zero events were included using a 0.5 continuity correction. DerSimonian and Laird random-effects models with inverse variance weighting were used to estimate pooled relative risks (RRs) and corresponding 95% CIs.[36] We prespecified the use of a random-effects approach because of the degree of clinical and statistical heterogeneity anticipated across RCTs. In secondary analyses, we pooled risk estimates for DVT and PE separately. All analyses were conducted using R version 3.5.0,[37] and we assessed the quality of evidence using the GRADEPro online platform.[38]

The amount of between-study heterogeneity was assessed using the I^2 statistic and incorporated in the estimation of 95% prediction intervals. The I^2 statistic describes the proportion of the overall variance that is due to between-study heterogeneity rather than due to chance. The prediction interval provides the range in which we can expect to find the estimated treatment effect of a subsequent RCT. We used a funnel plot and Egger's test to evaluate the potential presence of small-study effects (typically publication bias).

Sensitivity Analyses

We prespecified 11 sensitivity analyses to examine the robustness of our results. First, we pooled estimates using the Hartung and Knap extension of the random-effects model, which is designed for meta-analyses in which few studies (<10) are included.[39] Second, we used a fixed-effects approach with an inverse variance to determine how sensitive our results were to our

choice of modeling strategy. Third, to examine the impact of sparse data on our pooled estimates, we repeated our primary analysis using the Peto method,[40] which provides the least biased estimates with good 95% CI coverage when modeling sparse outcomes. Fourth, we repeated the meta-analysis without continuity correction for treatment groups with zero events to examine the impact of using a continuity correction for RCTs with zero events. Fifth, we stratified results by funding sources to assess its potential impact on reported outcomes. Sixth, we restricted our analyses to RCTs randomized the study participants into TRT or placebo arm. Finally, while we had pre-specified sensitivity analyses across the subgroup of studies stratified by the characteristics of the participants included (such as age, total serum testosterone level at baseline), study quality, duration of follow-up, and TRT formulation, route of administration, dose, and duration, these analyses were not conducted due to sparse data.

RESULTS

Search Results

A total of 5,014 articles were identified from our search of six databases and two clinical trial registries (**Supplementary Table 1**). After removing duplicates, 4,019 publications underwent title/abstract screening, 418 underwent full-text review, and 13 were included in this meta-analysis (**Figure 1**).

Study Characteristics

Table 1 describes the characteristics of the included RCTs. The 13 RCTs included 5,050 men, 2,636 of whom were randomized to TRT and 2,414 to placebo or active comparator. The sample size of included RCTs ranged from 101 to 790 men. Nine of the trials were published in peer-reviewed scientific journals, while the remaining 4 trials were identified in ClinicalTrials.gov. Eleven trials were placebo-controlled, and two used an active comparator.[41,42] The duration of TRT and follow-up ranged from 3-36 months. The characteristics of TRT varied across studies in terms of dose, duration, and route of administration. All studies were randomized by design; however, five studies had an unclear method of randomization. All trials but one (an open-label trial) blinded the study participants, researchers, or outcome assessors to treatment allocation. Most of the studies' primary outcome was total serum testosterone change from baseline. A total of 15 (0.6%) men in the TRT group and 12 (0.5%) in the placebo or active comparator group had VTE during follow-up. Most of the studies reported VTE as adverse events that were adjudicated by systematic assessment or a prespecified assessor. However, it is unclear whether the adjudication or systematic assessment included an objective assessment using diagnostic imaging. The VTE outcome classification was made following an intention-to-

treat (ITT) approach. Two studies were publicly funded, and 11 were fully or partially funded by industry.

Risk of Bias

Two of the studies had a low risk of bias, six studies had a moderate risk of bias, and five studies had a high risk of bias (**Table 2** and **Figures 2-3**). The high risk of bias was largely driven by the unclear or suboptimal measurement of VTE or unclear randomization. Potentially missing outcome data and deviation from the intended intervention domains also contributed to the high risk of bias. The overall quality of evidence according to the GRADE criteria[33] was low for the primary (VTE) and secondary outcomes (DVT and PE). We downgraded the quality of the evidence due to the imprecision of estimates, unclear randomization, and unclear outcome measurement (**Supplementary Table 2**).

Meta-Analysis Results

When data were pooled across RCTs, we did not find an increased risk of VTE among participants randomized to TRT compared to those randomized to placebo or active comparator (RR: 1.03, 95% CI: 0.49, 2.14; I^2: 0%; low-quality evidence) (**Figure 4** and **Supplementary Table 2**). The 95% prediction interval for VTE ranged from 0.49 to 2.14. Similarly, randomization to TRT was not associated with the risk of DVT (RR: 1.14, 95% CI: 0.46 to 2.82; I^2: 0%; low-quality evidence) or PE (RR: 0.81, 95% CI: 0.29, 2.26; I^2: 0%; low-quality evidence) (**Supplementary Table 2**, **Supplementary Figures 1-2**). The 95% prediction intervals were 0.44 to 2.90 for DVT and 0.29 to 2.26 for PE. The symmetric shape of the funnel plot and Egger's statistical test suggested that small-study effects were not present (**Figure 5**).

The sensitivity analyses examining different assumptions produced results that were consistent with those of our primary analysis (**Supplementary Figures 3-7**).

DISCUSSION

This systematic review and meta-analysis of RCTs was designed to determine the risk of VTE associated with the use of TRT among men. When study-specific estimates were pooled across 13 RCTs, we found no evidence of an increased risk of VTE with TRT. Similar results were obtained for DVT and PE and across several sensitivity analyses. We observed a high risk of bias and an overall low quality of evidence. While no evidence of an increased risk was observed, our estimates were accompanied by wide 95% CIs, and we cannot rule out a potential clinically important increased risk. Indeed, the width of prediction intervals with a Hartung and Knapp method indicates that the expected true effect of TRT on VTE could either be beneficial or detrimental in future RCTs. Consequently, while we have synthesized the totality of the evidence available from RCTs regarding this issue, there remains a need for additional large RCTs with a longer follow-up that specifically examine the risk VTE associated with TRT to further assess this potential drug safety issue.

A potential mechanism behind the purported VTE risk of TRT involves the presence of a 'procoagulant' state immediately after testosterone initiation.[43] Moreover, the potential role of testosterone in the regulation of platelet TXA2 receptors' expression might contribute to the thrombogenicity of androgenic steroids.[21] Older men with functional limitations have increased levels of factor VIII and D-dimer,[44] and a high testosterone level might increase susceptibility to VTE.[45]

Previous studies regarding the VTE risk of TRT have been inconclusive. Eight observational studies have examined this issue to date[23-25,46-50]. Two of these studies[24,25] found an increased risk of VTE in men treated with TRT, while the others did not[23,46-50]. These studies also identified heterogeneity in treatment effects in some sub-populations, with VTE risk

attenuated among men with clinical hypogonadism[24] and in men aged 65 years or over.[25] Previous systematic reviews of the VTE risk of TRT reported heterogeneous results.[12,26,27,51] A letter by Xu et al. described an increased risk of VTE with TRT (odds ratio [OR]: 5.94, 95% CI: 1.00-35.30) but this estimate was derived from only three RCTs.[27] Two other systematic reviews did not include all relevant RCTs.[12,26] Consistent with our findings, the 2020 evidence report for a Clinical Practice Guideline by the American College of Physicians presented a non-increased VTE risk with testosterone treatment in comparison to placebo.[51] Given the recent increased use of TRT globally[5] and the safety warnings emitted by the FDA,[13] Health Canada,[52] and Endocrine Society of Australia[53] about the risk of VTE in testosterone use, the present study adds to the body of evidence on the safety of TRT with respect to VTE.

This study has several strengths. First, with a comprehensive and rigorous search strategy developed in consultation with an experienced medical librarian, relevant articles were identified from the published scientific and grey literature. Second, we conducted several sensitivity analyses that confirmed the robustness of our primary results. Third, we assessed the risk of bias with the Cochrane Risk of Bias 2.0 tool[33] and the overall quality of evidence using GRADE[35,38]. Finally, we found no evidence of small-study effects, suggesting that publication bias is unlikely to have had an important impact on our results.

This study also has several potential limitations. First, the response rate from the authors of unpublished clinical trials (grey literature) was low. Among the eight completed RCTs registered in Clinical.Trials.gov without published results, only three authors responded to our queries. Second, VTE was rare, and treatment effects were therefore accompanied by wide 95% CIs. In addition, we were unable to conduct all prespecified sensitivity analyses given the sparse data. However, this represents the totality of the available evidence regarding the VTE risk of

TRT. Third, we aimed to assess the risk of VTE, an outcome primarily reported as part of the adverse event reporting of these RCTs. We were limited to the outcome definition used in the included trials; the use of different outcome definitions across trials represents a potentially important source of heterogeneity. In addition, the potential under-reporting of VTE events[26] might have biased the estimates toward the null. Although the proportion of lost-to-follow-up was low in these trials, it was not clear whether some of the men who were lost-to-follow-up experienced VTE events. Finally, it was not clear whether the included studies used pre-specified criteria to measure VTE-related events. Consequently, some outcome misclassification is possible.

CONCLUSIONS

Our systematic review and meta-analysis of RCTs suggests that TRT is not associated with an increased risk of VTE. However, estimates were accompanied by a wide 95% CIs, and a clinically important increased risk cannot be ruled out. Despite the limitations of the available evidence, the findings of this systematic review and meta-analysis contribute to the evolving body of evidence regarding the cardiovascular safety of TRT.

ACKNOWLEDGMENTS

We thank Andrea Quaiattini, a medical librarian at McGill University, for her help on the development of our search strategies and relevant articles identification.

SOURCES OF FUNDING

This study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. KBF is supported by a senior salary support award from the Fonds de recherche du Québec – Santé (FRQS; Quebec Foundation for Research - Health) and a William Dawson Scholar award from McGill University. HTA is supported by an FRQS Postdoctoral Training Award. VCB holds a Doctoral Training Award from the FRQS and a Drug Safety and Effectiveness Training (DSECT) Program Award funded by the Canadian Institutes of Health Research (CIHR) . CR is the recipient of a salary award from the FRQS.

DISCLOSURES

The authors declare no competing interest.

AUTHORS' CONTRIBUTIONS

HTA designed the study, conducted screening, extracted data, assessed quality, conducted the statistical analyses, and drafted the manuscript. VCB performed screening, data extraction, quality assessment, interpreted data, and critically reviewed the manuscript. KBF, CR, and VT contributed to study design and protocol development, interpreted data, and critically reviewed the manuscript for important intellectual content. KBF is the guarantor.

REFERENCES

1. Hackett G. An update on the role of testosterone replacement therapy in the management of hypogonadism. Ther Adv Urol 2016;8:147-60.
2. Mirone V, Debruyne F, Dohle G, et al. European Association of Urology Position Statement on the Role of the Urologist in the Management of Male Hypogonadism and Testosterone Therapy. Eur Urol 2017;72:164-7.
3. Wang C, Nieschlag E, Swerdloff R, et al. ISA, ISSAM, EAU, EAA and ASA recommendations: investigation, treatment and monitoring of late-onset hypogonadism in males. Int J Impot Res 2009;21:1-8.
4. Handelsman DJ. Global trends in testosterone prescribing, 2000-2011: expanding the spectrum of prescription drug misuse. Med J Aust 2013;199:548-51.
5. Baillargeon J, Kuo YF, Westra JR, Urban RJ, Goodwin JS. Testosterone Prescribing in the United States, 2002-2016. JAMA 2018;320:200-2.
6. Vigen R, O'Donnell CI, Baron AE, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. JAMA 2013;310:1829-36.
7. Finkle WD, Greenland S, Ridgeway GK, et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. PLoS One 2014;9:e85805.
8. Xu L, Freeman G, Cowling BJ, Schooling CM. Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials. BMCMed 2013;11:108.
9. Basaria S, Coviello AD, Travison TG, et al. Adverse events associated with testosterone administration. N Engl J Med 2010;363:109-22.

10. The U.S. Food and Drug Administration (FDA). Drug Safety Communication: FDA cautions about using testosterone products for low testosterone due to aging2018.
11. Jones RD, English KM, Jones TH, Channer KS. Testosterone-induced coronary vasodilatation occurs via a non-genomic mechanism: evidence of a direct calcium antagonism action. Clin Sci (Lond) 2004;107:149-58.
12. Corona G, Dicuio M, Rastrelli G, et al. Testosterone treatment and cardiovascular and venous thromboembolism risk: what is 'new'? J Investig Med 2017;65:964-73.
13. The U.S. Food and Drug Administration (FDA). FDA adding general warning to testosterone products about potential for venous blood clots. 2014 August 26, 2020.
14. Prince M, Glueck CJ, Shah P, et al. Hospitalization for pulmonary embolism associated with antecedent testosterone or estrogen therapy in patients found to have familial and acquired thrombophilia. BMC Hematol 2016;16:6.
15. Glueck CJ, Prince M, Patel N, et al. Thrombophilia in 67 Patients With Thrombotic Events After Starting Testosterone Therapy. Clinical and Applied Thrombosis/Hemostasis 2016.
16. Glueck CJ, Wang P. Testosterone therapy, thrombosis, thrombophilia, cardiovascular events. Metabolism: Clinical and Experimental2014.
17. Glueck CJ, Friedman J, Hafeez A, Hassan A, Wang P. Testosterone therapy, thrombophilia, and hospitalization for deep venous thrombosis-pulmonary embolus, an exploratory, hypothesis-generating study. Med Hypotheses 2015;84:341-3.
18. Matsuda K, Ruff A, Morinelli TA, Mathur RS, Halushka PV, Mo-Rinelli TA. Testosterone increases thromboxane A2 receptor density and responsiveness in rat aortas and platelets. Am J Physiol 267 1994.

19. Gonzales RJ, Ghaffari AA, Duckles SP, Krause DN. Testosterone treatment increases thromboxane function in rat cerebral arteries. American Journal of Physiology - Heart and Circulatory Physiology 2005.
20. Ajayi AAL, Halushka PV. Castration reduces platelet thromboxane A2 receptor density and aggregability. QJM - Monthly Journal of the Association of Physicians 2005.
21. Ajayi A, Mathur R, Halushka P. Coronary Heart Disease/Myocardial Infarction: Testosterone Increases Human Platelet Thromboxane A sub 2 Receptor Density and Aggregation Responses. Circulation1995.
22. Freedman J, Glueck CJ, Prince M, Riaz R, Wang P. Testosterone, thrombophilia, thrombosis. Translational Research 2015.
23. Baillargeon J, Urban RJ, Morgentaler A, et al. Risk of Venous Thromboembolism in Men Receiving Testosterone Therapy. Mayo Clin Proc 2015;90:1038-45.
24. Martinez C, Suissa S, Rietbrock S, et al. Testosterone treatment and risk of venous thromboembolism: population based case-control study. BMJ 2016;355:i5968.
25. Walker RF, Zakai NA, MacLehose RF, et al. Association of Testosterone Therapy With Risk of Venous Thromboembolism Among Men With and Without Hypogonadism. JAMA Intern Med 2019.
26. Houghton DE, Alsawas M, Barrioneuvo P, et al. Testosterone therapy and venous thromboembolism: A systematic review and meta-analysis. Thromb Res 2018;172:94-103.
27. Xu L, Schooling CM. Differential risks in men and women for first and recurrent venous thrombosis: the role of genes and environment: comment. J Thromb Haemost 2015;13:884-6.
28. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4:1.

29. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 2010;8:336-41.
30. Glanville JM, Lefebvre C, Miles JN, Camosso-Stefinovic J. How to identify randomized controlled trials in MEDLINE: ten years on. J Med Libr Assoc 2006;94:130-6.
31. Ho GJ, Liew SM, Ng CJ, Hisham Shunmugam R, Glasziou P. Development of a Search Strategy for an Evidence Based Retrieval Service. PLoS One 2016;11:e0167170.
32. Decaroli MC, Rochira V. Aging and sex hormones in males. Virulence 2017;8:545-70.
33. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ (in press) 2019.
34. Corona G, Isidori AM, Buvat J, et al. Testosterone supplementation and sexual function: a meta-analysis study. J Sex Med 2014;11:1577-92.
35. Schünemann H, Brożek J, Guyatt G, Oxman A, editors. GRADE handbook for grading quality of evidence and strength of recommendations. . The GRADE Working Group; 2013.
36. DerSimonian R, Kacker R. Random-effects model for meta-analysis of clinical trials: an update. Contemp Clin Trials 2007;28:105-14.
37. R Development Core Team. R: A language and environment for statistical computing. 3.5.0 ed. Vienna, Austria. : The R Foundation for statistical computing 2018.
38. McMaster University dbEP, Inc.). GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. 10 ed. Hamilton (ON)2015.
39. Jackson D, Law M, Rucker G, Schwarzer G. The Hartung-Knapp modification for random-effects meta-analysis: A useful refinement but are there any residual concerns? Stat Med 2017;36:3923-34.

40. Brockhaus AC, Bender R, Skipka G. The Peto odds ratio viewed as a new effect measure. Stat Med 2014;33:4861-74.
41. Indevus_Pharmaceuticals. Long-term Safety Study of Intramuscular Injections of 750 mg and 1000 mg Testosterone Undecanoate in Hypogonadal Men (TU): ClinicalTrials.gov; 2017.
42. Swerdloff. A Study of Oral Testosterone Undecanoate (TU) in Hypogonadal Men (inTUne): ClinicalTrials.gov; 2018.
43. Anderson RA, Ludlam CA, Wu FC. Haemostatic effects of supraphysiological levels of testosterone in normal men. Thromb Haemost 1995;74:693-7.
44. Walston J, McBurnie MA, Newman A, et al. Frailty and activation of the inflammation and coagulation systems with and without clinical comorbidities: results from the Cardiovascular Health Study. Arch Intern Med 2002;162:2333-41.
45. Basaria S, Collins L, Dillon EL, et al. The safety, pharmacokinetics, and effects of LGD-4033, a novel nonsteroidal oral, selective androgen receptor modulator, in healthy young men. J Gerontol A Biol Sci Med Sci 2013;68:87-95.
46. Argalious MY, You J, Mao G, et al. Association of Testosterone Replacement Therapy and the Incidence of a Composite of Postoperative In-hospital Mortality and Cardiovascular Events in Men Undergoing Noncardiac Surgery. Anesthesiology 2017;127:457-65.
47. Cole AP, Hanske J, Jiang W, et al. Impact of testosterone replacement therapy on thromboembolism, heart disease and obstructive sleep apnoea in men. BJU Int 2018;121:811-8.

48. Debruyne FM, Behre HM, Roehrborn CG, et al. Testosterone treatment is not associated with increased risk of prostate cancer or worsening of lower urinary tract symptoms: prostate health outcomes in the Registry of Hypogonadism in Men. BJU Int 2017;119:216-24.

49. Maggi M, Wu FC, Jones TH, et al. Testosterone treatment is not associated with increased risk of adverse cardiovascular events: results from the Registry of Hypogonadism in Men (RHYME). Int J Clin Pract 2016;70:843-52.

50. Sharma R, Oni OA, Chen G, et al. Association Between Testosterone Replacement Therapy and the Incidence of DVT and Pulmonary Embolism: A Retrospective Cohort Study of the Veterans Administration Database. Chest 2016;150:563-71.

51. Diem SJ, Greer NL, MacDonald R, et al. Efficacy and Safety of Testosterone Treatment in Men: An Evidence Report for a Clinical Practice Guideline by the American College of Physicians. Ann Intern Med 2020;172:105-18.

52. Health Canada. Information Update - Possible cardiovascular problems associated with testosterone products. Accessed at http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2014/40587a-eng.php. Access date: February 22, 2018. 2014.

53. Yeap BB, Grossmann M, McLachlan RI, et al. Endocrine Society of Australia position statement on male hypogonadism (part 1): assessment and indications for testosterone therapy. Med J Aust 2016;205:173-8.

Table 1. Characteristics of randomized controlled trials reporting the risk of venous thromboembolism with testosterone replacement therapy versus placebo or active comparator.

Study population				Intervention						Outcome			Analysis
Author, Year	**Sample size**	**Age (Mean)**	**Baseline Serum TT**	**Dose**	**Duration of TT Rx**	**RoA**	**Duration of FUP**	**Method of randomization**	**Blinding**	**Primary Outcome**	**Outcome of the review**	**LTF**	
Behre *et.al*, 2012	362	65.6*	<15nmol/l	5mg	6m	Transdermal	12m	Computer generated	Double-blind	Change in lean body mass	DVT	Testosterone=8.2% & Placebo=13.4%	ITT
Bhasin *et.al*, 2017	306	67.6	Hypogonadal	7.5mg	36m	Transdermal	36m	Computer generated	Double-blind	Change in CAIMT	PE	Testosterone=3.2% & Placebo=2.6%	ITT
Brock *et.al* (3 months), 2016	596	55.3	300-1050ng/dl	60mg	3m	Transdermal	3m	Computer generated	Triple-blind	Total serum testosterone	VT & PE	Testosterone=1.7% & Placebo=2.4%	ITT
Brock *et.al (9 months)*, 2016	596	54.6	Hypogonadal	60mg	9m	Transdermal	9m	Computer generated	Triple-blind	Total serum testosterone	VT & PE	Testosterone=2.3% & Placebo=2.8%	ITT
Eli Lilly and company, 2015	715	55.3	<300ng/dl	60mg	3m	Transdermal	3m	Unclear	Triple-blind	Total serum testosterone	DVT & PE	Testosterone=1.8% & Placebo=1.8%	Unclear (ITT assumed)
Gluud *et.al*, 1987	126	NR	NR	200mg	36m	Oral	28m	Random numbers	Double-blind[$]	Liver morphology changes	BCS	All=10.4%	Unclear (ITT assumed)
Gluud *et.al*, 1986	221	53.0	NR	100mg	36m	Oral	30m	Random numbers	Double-blind[$]	All-cause mortality	VT	Testosterone=11.2% & Placebo=9.2%	Unclear (ITT assumed)

Indevus Pharmaceuticals, 2017	524	54.4	NR	1000mg	36m	Intramuscular	36m	Unclear	Open-label	Total serum testosterone	DVT	All=2.5%	ITT
Sinclair *et.al*, 2016	101	55.0	<12nmol/l	100mg	10m	Intramuscular	10m	Unclear	Triple-blinded	Lean muscle mass	VT	All=9.9%	Unclear (ITT assumed)
Snyder *et.al*, 2016	790	72.2	<275ng/dl	5gm	12m	Transdermal	12m	Permuted blocks (Size of 4)	Quadriple-blinded	Sexual activity and walking distance	VTE	Testosterone=4.8% & Placebo=5.3%	Unclear (ITT assumed)
Srinivas-Shanker *et.al*, 2010	262	73.8	≤345ng/dl	50mg	6m	Transdermal	6m	Computer generated	Qudriple blinded	Muscle strengths, physical function, body composition and QoL	PE	Testosterone=6.9% & Placebo=5.3%	ITT
Swerdloff *et.al*, 2018	222	52.0	Hypogonadal	474mg	3.5m	Oral	3.5m	Unclear	Open-label	Total serum testosterone	VT	Testosterone=1.2% & Placebo=0%	ITT
Tan *et.al*, 2013	114	NR	≤12nmol/l	1000mg	12m	Intramuscular	12m	Unclear	Triple-blinded[#]	Total serum testosterone	DVT & PE	Testosterone=3.3% & Placebo=0%	ITT

*Testosterone=69.1±6.6 and Placebo=62.1±6.3; NR: Not reported; [$] Patients and outcome assessors were blinded; [#] Unblinding was only performed in the event of a serious adverse event; CAIMT: Carotid artery intima-media thickness; DVT: Deep vein thrombosis; FUP: Follow-Up; ITT: Intention-to-Treat; LTF: Lost-to-Followup; m: Months; PE: Pulmonary embolism; QoL: Quality of life; RoA: Route of Administration; VT: Venous thrombosis; VTE: Venous thromboembolism; TT: Testosterone; Rx: Treatment;

Table 2. The overall and domain-specific risk of bias among randomized controlled trials reporting the risk of venous thromboembolism with testosterone replacement therapy versus placebo or active comparator.

	Randomization process	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported result**	**Overall Bias**
Total number of studies = 13*						
Low risk	43.0	53.7	89.9	34.1	64.4	14.4
Some concerns	30.3	39.4	0	29.2	35.6	41.9
High risk	26.7	6.9	10.1	36.8	0	43.7

Data are reported as percentages.

***** Assignment to intervention (the 'intention-to-treat' effect)

FIGURE LEGENDS

Figure 1. Flow diagram describing the selection of randomized controlled trials reporting the risk of venous thromboembolism with testosterone replacement therapy versus placebo or active comparator.

Figure 2. Percentage of the overall and domain-specific risk of bias of randomized controlled trials reporting the risk of venous thromboembolism with testosterone replacement therapy versus placebo or active comparator.

Figure 3. The risk of bias in randomized controlled trials reporting the risk of venous thromboembolism with testosterone replacement therapy versus placebo or active comparator.

Figure 4. Pooled relative risk of venous thromboembolism in men using testosterone replacement therapy versus placebo or active comparator.

Figure 5. Enhanced funnel with the risk ratios and standard error from randomized controlled trials reporting the risk of venous thromboembolism with testosterone replacement therapy versus placebo or active comparator. Regression test for funnel plot asymmetry with mixed-effects meta-regression model: $z = 0.1207$, $p = 0.9039$.

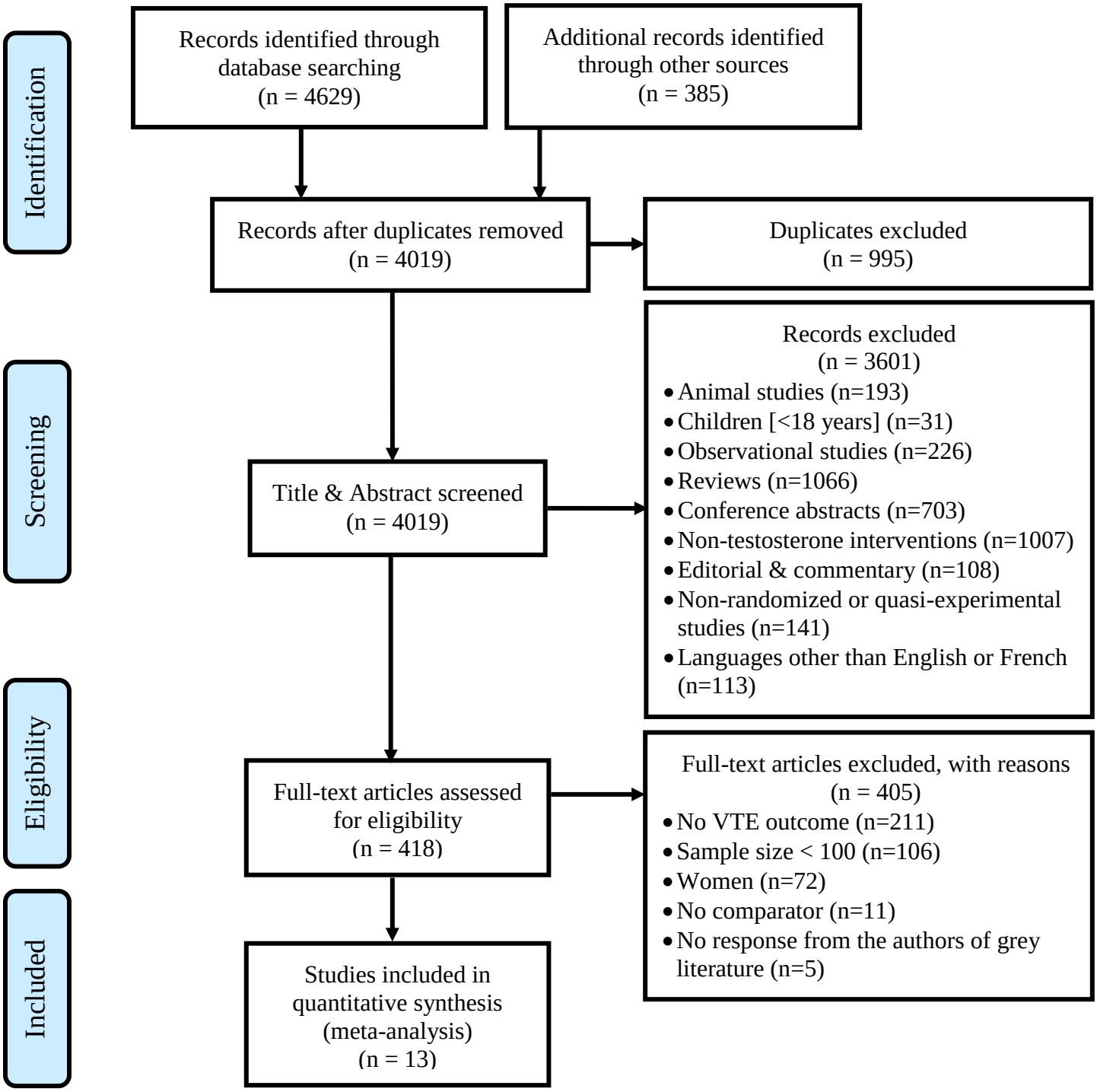
Identification
Screening
Eligibility
Included
Records identified through database searching (n = 4629)
Additional records identified through other sources (n = 385)
Records after duplicates removed (n = 4019)
Duplicates excluded (n = 995)
Title & Abstract screened (n = 4019)
Records excluded (n = 3601)
Animal studies (n=193)
Children [<18 years] (n=31)
Observational studies (n=226)
Reviews (n=1066)
Conference abstracts (n=703)
Non-testosterone interventions (n=1007)
Editorial & commentary (n=108)
Non-randomized or quasi-experimental studies (n=141)
Languages other than English or French (n=113)
Full-text articles assessed for eligibility (n = 418)
Full-text articles excluded, with reasons (n = 405)
No VTE outcome (n=211)
Sample size < 100 (n=106)
Women (n=72)
No comparator (n=11)
No response from the authors of grey literature (n=5)
Studies included in quantitative synthesis (meta-analysis) (n = 13)

Figure 1.

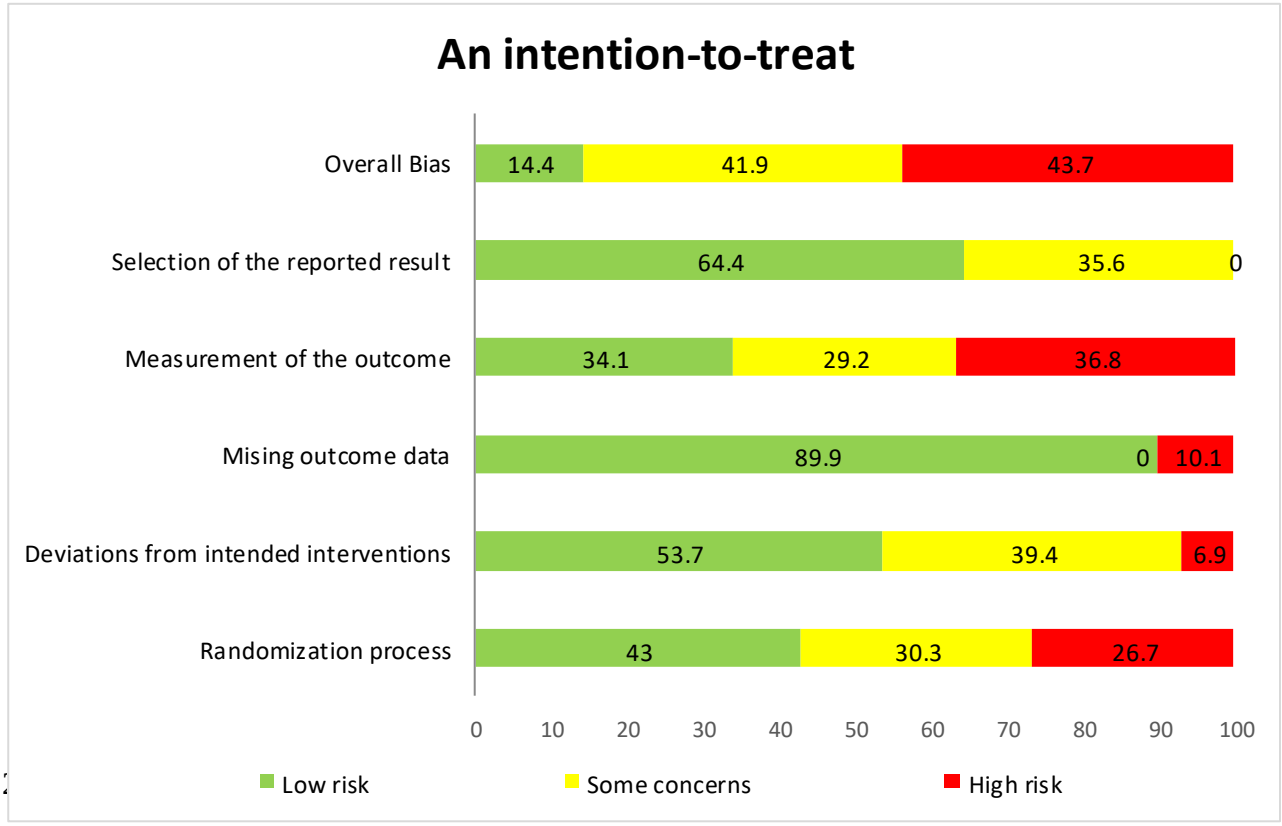
An intention-to-treat
Overall Bias
14.4
41.9
43.7
Selection of the reported result
64.4
35.6
0
Measurement of the outcome
34.1
29.2
36.8
Mising outcome data
89.9
0
10.1
Deviations from intended interventions
53.7
39.4
6.9
Randomization process
43
30.3
26.7
0
10
20
30
40
50
60
70
80
90
100
Low risk
Some concerns
High risk

Figure 2


Study
Weight
Randomization process
Deviations from intended interventions
Missing outcome data
Measurement of the outcome
Selection of the reported result
Overall Bias
Behre et.al, 2012 5.27
Snyder et.al, 2016 31.46
Sirnivas-Shankar et.al, 2010 5.28
Swedloff et.al, 2018 5.3
Tan et.al, 2013 3.53
Brock et.al (9 months), 2016 5.87
Brock et.al (3 months), 2016 5.85
Eli Lilly, 2015 5.85
Gluud et.al, 1987 5.31
Gluud et.al, 1986 6.18
Bhasin et.al, 2017 5.28
Indevus Pharma, 2017 5.26
Sinclair et.al, 2016 9.59
Low risk
Some
High

Figure 3.

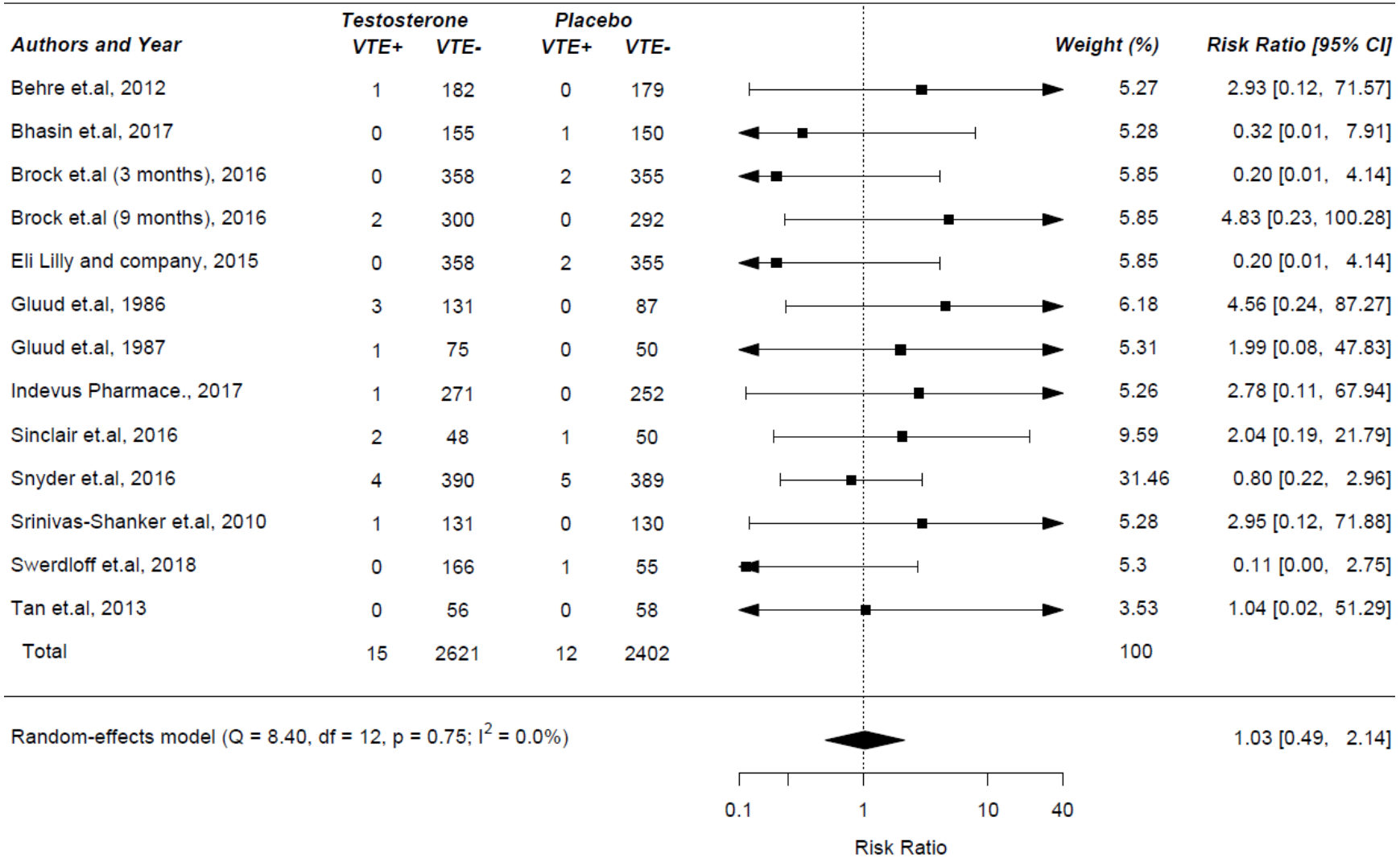
Testosterone
Placebo
Authors and Year
VTE+ VTE- VTE+ VTE-
Weight (%)
Risk Ratio [95% CI]
Behre et.al, 2012 1 182 0 179 5.27 2.93 [0.12, 71.57]
Bhasin et.al, 2017 0 155 1 150 5.28 0.32 [0.01, 7.91]
Brock et.al (3 months), 2016 0 358 2 355 5.85 0.20 [0.01, 4.14]
Brock et.al (9 months), 2016 2 300 0 292 5.85 4.83 [0.23, 100.28]
Eli Lilly and company, 2015 0 358 2 355 5.85 0.20 [0.01, 4.14]
Gluud et.al, 1986 3 131 0 87 6.18 4.56 [0.24, 87.27]
Gluud et.al, 1987 1 75 0 50 5.31 1.99 [0.08, 47.83]
Indevus Pharmace., 2017 1 271 0 252 5.26 2.78 [0.11, 67.94]
Sinclair et.al, 2016 2 48 1 50 9.59 2.04 [0.19, 21.79]
Snyder et.al, 2016 4 390 5 389 31.46 0.80 [0.22, 2.96]
Srinivas-Shanker et.al, 2010 1 131 0 130 5.28 2.95 [0.12, 71.88]
Swerdloff et.al, 2018 0 166 1 55 5.3 0.11 [0.00, 2.75]
Tan et.al, 2013 0 56 0 58 3.53 1.04 [0.02, 51.29]
Total 15 2621 12 2402 100
Random-effects model (Q = 8.40, df = 12, p = 0.75; I2 = 0.0%) 1.03 [0.49, 2.14]
0.1
1
10
40
Risk Ratio

Figure 4.

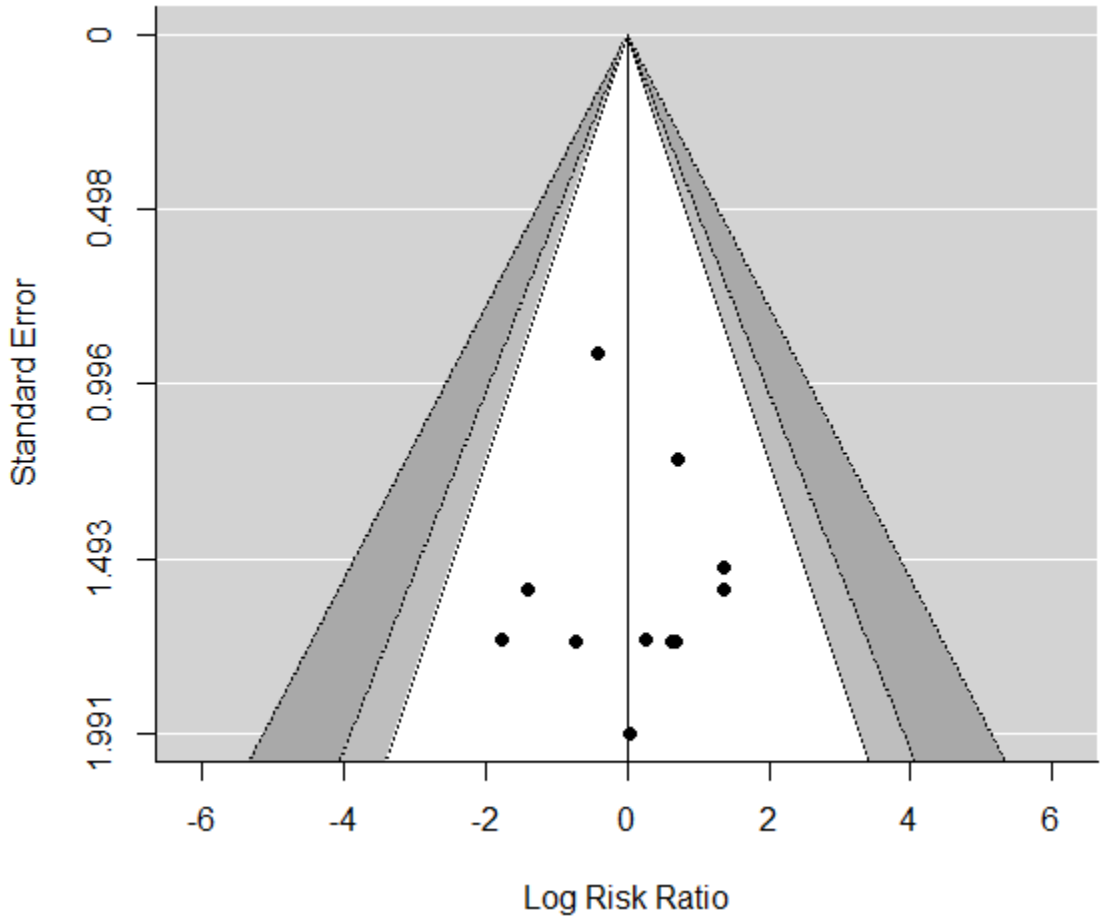

Figure 5.