

Cardiovascular Risk Associated with Male Testosterone Therapy

By

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A Capstone Paper submitted to the faculty of
the University of North Carolina at Chapel Hill
in partial fulfillment of the requirements
for the degree of Master of Health Sciences
in the Physician Assistant Program

Chapel Hill

November 2017

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Background:

Testosterone therapy, also known as male hormone replacement therapy has commonly been prescribed for older men since the 1950's. Low testosterone (low T) in men has been linked with elevated cardiovascular risk factors, cardiovascular events, and increased cardiovascular mortality¹. However, in 2014 the Food and Drug Administration (FDA) issued a warning regarding therapeutic testosterone use for age related hypogonadism or low T regarding increased cardiovascular related events and stroke². Although studied extensively, providers continue to disagree as to its safety and effectiveness especially considering this recent recommendation. Therefore, the purpose of this clinical review is to discuss diagnosis and treatment options for men with low T while evaluating systematic reviews analyzing cardiovascular risk.

Unlike female menopause, male hypogonadism does not universally develop in men. Low T, also known as hypogonadism or andropause, is associated with a lower quality of life and is currently estimated to affect as many as 38-40% of men in their lifetime³. To treat men for andropause, Testosterone therapy (TTh) is prescribed in several different forms such as intramuscular (IM) injections, topical creams, subcutaneous (SC) pellets, oral pills, and transdermal patches. With sales projected to reach 3.2 billion by 2022⁴, TTh is marketed to older men to treat multiple symptoms including: 1) fatigue, 2) mood, 3) muscle mass, 4) strength, and 5) sexual dysfunction as well as prevention of worsening heart disease⁵. But, in multiple reviews the conclusion is that there is little benefit that outweighs the risks associated with TTh. These risks include cardiovascular events such as myocardial infarction (MI) and stroke as well as prostatic hyperplasia, and cancer. With the widespread use of TTh, more definitive determinations need to be made regarding the potential dangers of TTh.

It is important to define male hypogonadism. There are an extensive range of natural and disease processes responsible for hypogonadism in men, normal aging being the most common cause. Normal secretion of testosterone is regulated by the hypothalamic-pituitary-gonadal axis. Approximately every 90 minutes, the hypothalamus secretes gonadotropin releasing hormone (GnRH) to the pituitary which releases luteinizing hormone (LH) to the testicles where Leydig cells then release testosterone. Any disruption in this process can lead to hypogonadism. Primary hypogonadism refers to dysfunction in the testicles, while secondary hypogonadism refers to dysfunction in the hypothalamus or pituitary ⁶.

Diagnosis of Hypogonadism:

There has been debate over what range of testosterone levels indicate clinically relevant hypogonadism and the subsequent need for TTh. The most common distinction currently in use is serum testosterone levels < 300 ng/dL ⁷. However, the ranges considered normal may be broader. A new systematic review of previous data verified a new range from 2.5% at 264 ng/dL to the 97% at 916 ng/dL, with a median of 530 ng/dL by cross-calibration of assays from four major epidemiological studies⁸.

The diagnosis of male hypogonadism begins with a symptomatic patient presentation with complaints that may include: 1) low libido, 2) decreased sexual activity, 3) reduction in spontaneous erections, 4) gynecomastia, and 5) loss of body hair. When reproduction is a goal, a patient may present with infertility and low sperm counts. According to the European Male Aging Study (EMAS), the most sensitive triad of symptoms related to physiologically low T levels are reduced sexual fantasies, reduced nocturnal and morning erections, and erectile dysfunction⁹. Associated symptoms include fatigue, increased body fat, decreased muscle mass,

and decreased overall sense of wellbeing. Patients presenting with these complaints are therefore most appropriate to screen for low testosterone¹⁰. Conversely, it is not recommended to screen asymptomatic men for low T.

Once a patient is identified appropriate for screening, the total serum testosterone is tested in the morning with a repeat test to confirm since up to 30% of men can have normal testosterone level on repeat testing¹⁰. Free or bioavailable testosterone levels should also be tested to determine if an issue with sex hormone-binding globulin (SHBG) is suspected. A normal serum free testosterone ranges in healthy individuals from 5–9 pg/ml (0.17–0.31 nmol/liter)¹⁰. Conditions associated with increased SHBG include aging, hepatic cirrhosis, obesity, diabetes, and hyperthyroidism as well as use of anti-convulsant and estrogens¹⁰. The presence of large amounts of SHBG will bind free testosterone, preventing its use by the body. Once morning low testosterone is confirmed, LH and FSH levels should be checked to determine if the source of deficiency is primary or secondary. Low testosterone with elevated LH and FSH levels indicates a primary dysfunction involving the testes. Low testosterone and low or normal levels of LH and FSH indicates a secondary dysfunction from the hypothalamus and/or pituitary. The current acceptable testosterone level to treat is <280-300 ng/dL¹⁰.

Treatment of Hypogonadism:

Currently there is no evidence that any specific modality of treatment has greater therapeutic effect or more side effects. The choice of form of treatment is left to provider and patient preference. According to the 2010 Endocrine Society clinical practice guidelines¹⁰, choices of testosterone treatments include 1) injectables, 2) oral pills, 3) creams and gels, 4) transdermal patches, 5) buccal tablets, and 6) implantable pellets. Injectable choices are

testosterone enanthate or cypionate 75-100mg weekly or 150-200mg every two weeks.

Testosterone undecanoate 1000 mg every 12 weeks. Oral testosterone undecanoate 40mg – 80mg taken once, twice, or three times daily. Transdermal testosterone patches are 2.5 mg and can be applied to the back, thigh, or upper arm. 5 to 10 grams of 1% testosterone gel is applied to the chest daily. 30 milligram testosterone tablets are applied to the buccal mucosa every 12 hours. Finally, testosterone pellets in various dosages can be injected under the skin every 3 to 6 months.

Methods:

In order to evaluate the current literature on cardiovascular risk associated with TTh, a study search was conducted through Pubmed, TRIP database, Cochrane Library, and Clinical Key utilizing key terms [**testosterone, therapy, cardiovascular, risk, systematic review, meta-analysis**]. The search was restricted to systematic reviews with meta-analysis within the last 10 years (2007 – 2017). Selected studies included only those primarily reviewing placebo-controlled randomized control trials (RCT's) of testosterone therapy with meta-analysis where evaluation of cardiovascular risk and/or events was the primary or secondary outcome of the study or one of the study arms. For each review we have reproduced the meta-analysis reported excluding Haddad et al. Forest plots of meta-analysis located in appendix 1.

Results

The above search criteria from Pubmed, TRIP database, Cochrane library of systematic reviews, and Clinical key yielded 7 systematic reviews with meta-analysis that met inclusion criteria evaluating TTh association with cardiovascular related events compared to placebo.

Haddad et al¹¹ (2007) conducted a systematic review and meta-analysis of only published RCT's to assess cardiovascular (CV) risk factors, CV events, and CV end points for TTh vs placebo. The study reviewed 30 RCT's from 1966 to 2004, with total population of 1642 men, 808 receiving TTh. Baseline low testosterone levels were defined as <300 ng/dL or 10.4 nmol/L. Quality assessment was determined based on the randomization, concealment of allocation, blinding, and loss to follow up. The authors noted that overall study quality was difficult to ascertain due to scant reporting on methods to limit bias. A full 20% of the studies inadequately reported allocation concealment and 9% did not address loss to follow up. No additional information pertaining to quality and bias assessment was divulged. The authors did not specify GRADE criteria, however, they stated that the available evidence is inconsistent, imprecise, and poorly reported. Statistical analysis for the meta-analysis was conducted using the random-effects method and I^2 statistic for heterogeneity across studies. Results of the study regarding CV events with TTh revealed an odds ratio (OR) of 1.82 (95% CI, 0.78 to 4.23) slightly favoring placebo.

Fernandez-Balsells et al¹² (2010) evaluated death, CV events, prostatic effects, and erythrocytosis adverse effects of TTh with a systematic review and meta-analysis of comparative RCT's and non-randomized control trials. Cardiovascular events evaluated included death, coronary events, stroke, and peripheral vascular events. A total of 51 studies were included in the review. Inclusion criteria required comparison of TTh to placebo in adult men with low or low to normal testosterone levels for a minimum of 3 months. Baseline testosterone levels were rated low if <300 ng/dL or 10.4 nmol/l. Exclusions were made for studies with additional hormone or

drug administration as well as outcomes not of interest. Studies covered 2003 to 2008 initially then expanded to include studies from 1981 to 2004 for HIV/AIDS population inclusion. GRADE criteria were used to evaluate quality of evidence for the randomized trials. Assessment was completed for randomization, allocation concealment, blinding, and loss to follow up. Quality of the studies included was deemed to be of low to medium quality. Twenty-eight studies failed to report allocation concealment and 34 did not report blinding of outcome assessors. Meta-analysis estimated relative risk (RR) for dichotomous outcomes and weighted mean difference for continuous outcomes pooled across studies using the random-effects model. Heterogeneity was used across studies using I^2 statistic for inconsistency. Overall, results for cardiovascular outcomes showed no significant differences between testosterone vs placebo groups (**figure 1**).

Xu et al¹³ (2013) utilized 27 RCT's totaling 2994 men comparing TTh to placebo for cardiovascular events for >12 weeks. Inclusion criteria consisted of randomized, placebo-controlled trials that evaluated cardiovascular events by study arm with testosterone as the sole hormone administered. Exclusion criteria included studies that only reported events in the TTh arm and not the placebo as well as trials of less than 12 weeks. Cardiovascular events included any reportable by the authors with serious events defined as death, cardiac hospitalization, medical/surgical intervention, myocardial infarction, coronary artery disease (CAD), unstable angina, arrhythmias, stroke, or congestive heart failure. Study search was conducted through 2012. Quality assessment evaluated randomization, allocation concealment, blinding, and masking utilizing the Delphi list. While the authors did not give a direct quality rating, quality analysis showed high potential for publication bias, blinding, and lack of detailed reporting on

CV-related events indicating low to moderate quality of evidence. Funnel plots with trim and fill assessed publication bias which suggested trials favoring placebo may be absent. Random effects model I^2 statistic was used to assess heterogeneity with fixed effects models for I^2 below 30%. Meta-analysis regression with inverse variance weighing was utilized for consistency. Results indicated an increase of cardiovascular events with TTh in the fixed effect model (OR 1.54, 95% CI 1.09 to 2.18). Trim and fill revised the OR to 1.69 (95% CI 1.21 to 2.38). When isolating serious events only, the OR was 1.61 (95% CI 1.01 to 2.56) with a trim and fill OR 2.01 (95% CI 1.30 to 3.14). Overall combined cardiovascular events resulted in an OR 1.57 (95% 0.78 to 3.13) (**figure 2.**). A further subset evaluation by this study found that trials funded by the pharmaceutical industry resulted in half the cardiovascular events of non-industry funded studies (4% vs. 8%). The authors reported little heterogeneity in the studies with I^2 at 7.8%.

Corona et al¹⁴ (2014) performed a systematic review and meta-analysis on RCT's on the effect of TTh on cardiovascular events from Jan. 1969 to Jan. 2014. Seventy-five RCT's utilizing 5464 men for a mean duration of 34 weeks were evaluated. Mean age was 59.9 years with baseline testosterone levels at 11.2 nmol/l (~320 ng/dL). Inclusion criteria consisted of placebo-controlled RCT's comparing TTh to placebo for CV events. Exclusions included studies not specifically stating CV events, androgens other than testosterone, simultaneous therapeutic drug use, and use of phosphodiesterase type 5 inhibitors. Specifically, the study's primary outcome was to identify the effect of TTh on new major adverse cardiovascular events (MACE) with secondary outcome reporting of all CV related events codified by ICD-10 criteria. MACE was defined as CV death, MI, stroke, acute coronary syndrome (ACS) or heart failure (HF). Quality assessment was made using Cochrane criteria and GRADE on randomization, allocation

concealment, blinding, loss to follow up, intention to treat analysis, and missing outcome data analysis. Further assessment was made regarding funding, population selection, and route of TTh administration. The overall quality of included RCTs graded as moderate to high quality, with 9 of the studies grading low or very low quality. Heterogeneity was assessed by I^2 statistics with random-effects model. Meta-regression analysis and funnel plots were used to test the effect of TTh related MACE and publication bias. Results of the study indicated no significant increase in MACE (OR 1.01 95% CI 0.57 to 1.77) or CV related events (OR 1.07 95% CI 0.69 to 1.65) (**figure 3.**). Further analysis of subpopulations for elderly, pre-existing cardiovascular disease (CVD), frailty, T-levels, duration, and funding did not show a statistically significant difference in MACE.

Borst et al¹⁵ (2014) completed a dual meta-analysis testing both CV adverse effects and the effect of TTh on serum testosterone and dihydrotestosterone (DHT). The primary outcome for the study was identified as any CV related events defined by the RCTs per ICD-10 codes. Secondary outcomes looked at the serum T and DHT levels following TTh delivered by various routes of administration. The CV adverse effects arm identified 35 placebo-controlled RCTs (3703 men >45yrs) for inclusion reporting CV-related events for both TTh and placebo groups after use greater than 12 weeks. Thirty-two of the RCTs reported on testosterone and DHT levels. Studies with testosterone suppression prior to TTh and durations of less than 12 weeks were excluded. The meta-analysis followed the PRISMA checklist. Quality assessment was evaluated using the Delphi list criteria for randomization, allocation, and blinding. Overall quality is rated moderate to low quality due to risk of bias. The meta-analysis was performed using the weighted random effects method due to sample size and RR vs OR was employed.

Results of the study showed CV-related events at 6.2% for TTh and 5.5% for placebo. Among men in the TTh arm, RR for CV events was 1.28 (95% CI 0.76 to 2.13, $p=0.34$) (**figure 4.**). Interestingly, CV events did vary by route of TTh administration. Oral TTh significantly increased CV events RR 2.20 (95% CI 1.45 to 3.35, $P=0.32$) (**figure 4.**). No significant increase in risk was associated with intramuscular or transdermal testosterone. Evaluation of serum T and DHT levels showed IM delivery raised the levels congruently while both transdermal and oral compounds increased DHT levels significantly compared to testosterone. The authors finding concerning oral TTh risk was speculated as due to the expression of 5- α reductase in the skin and liver which converts testosterone to DHT. Additionally, higher levels of DHT have recently been independently implicated to increases in CV risk¹⁶. Limitations of this study include ambiguity defining CV adverse effects. Data on oral preparations was also limited and must be interpreted with caution.

Albert & Morley¹⁷ (2016) This study's primary aim was to determine CV events related to age and mode of administration. The systematic review and meta-analysis identified 45 RCT's, 35 from previous studies included in Xu et al, Borst et al, and Corona et al. An additional 10 studies from 2013 to 2016 were included that were not a part of the Xu and Borst list. A total of 5328 patients with a mean age of 63.3 years were followed for an average of 10.6 months at T levels of <12 nmol/l (~345 ng/dL). CV events were defined prior to initiation as death, MI, ACS, percutaneous coronary intervention, coronary bypass, syncope, arrhythmia, and hospitalization for HF/stroke. GRADE criteria were used to evaluate quality (rated high for large RCT's, Medium for post hoc analysis of CV events, and low for observational or retrospective studies). Funnel plots were used to identify publication bias and heterogeneity was calculated by I^2 (0-

30% low, 30-60% mod). Meta-analysis assessed mean difference with a fixed effect model. Overall results of the study showed no statistically significant increase in CV related events (RR 1.10 95% CI 0.86 to 1.46, P=0.45) (**figure 5**). Outcomes did not change for overall risk based on TTh mode, initial T levels, or therapeutic T levels. However, a higher association of risk was prevalent in the first 12 months of TTh with RR 1.79 95% CI 1.13 to 2.82, p=0.012). Among older men (>65) within the first 12 months RR was 2.90 (95% CI 1.35 to 6.21, p=0.006, I²=0%). No publication bias was found based on funnel plot analysis. Limitations of this study include reporting using poorly defined CV-related events, as well as no identifiable predisposing factors for the age-related findings within the first 12 months.

Alexander et al¹⁸ (2017) reviewed 39 RCTs and 10 observational studies with the primary goal of evaluating associated increased risk of serious CV events. Meta-analysis evaluated data from 30 RCTs (3230 patients). Inclusion criteria encompassed both RCT's and observational studies of men 18 years and older (50 – 60 mean age range) with a minimum of 10 participants comparing pre- and post-treatment testosterone levels to placebo or comparator for >3 days. Exclusions included studies containing patients with HIV, cancer, end-stage renal disease, schizophrenia, or primary hypogonadism. Primary outcomes reviewed were all cause mortality, MI, or stroke. Secondary outcomes identified other CV events such as arrhythmias, coronary angiography, pulmonary embolism (PE), or venous thrombosis. Quality assessment for RCT's was made using Cochrane risk of bias to evaluate demographics, details of treatment/control groups, randomization, masking, and funding. Non-randomized studies were evaluated by Newcastle and Ottawa scale methods. Strength of evidence was conducted by GRADE criteria for imprecision, inconsistency, indirectness, and publication bias. Overall

quality was rated as low due to risk of bias in RCTs and imprecision. Heterogeneity was assessed by I^2 statistics with $>50\%$ being substantial to remove from quantitative analysis. Meta-analysis used the fixed-effects model to calculate OR with 95% CI. Publication bias was evaluated by funnel plot and Eggers and Beggs-Mazumdar test, with >10 studies included. Composite results of MI, stroke, and death showed no significant increase in risk OR 0.96 (95% CI 0.65 to 1.42, $I^2=35.9\%$) (figure 6.). Individually, no increased risk was associated with MI OR 0.87 (95% CI 0.39 to 1.93, $I^2=36.4\%$), stroke OR 2.17 (95% CI 0.63 to 7.54, $I^2=29.9\%$), or death OR 0.88 (95% CI 0.55 to 1.41, $I^2=7.7\%$). Subgroup analysis for patients with type II diabetes (T2DM) or pre-existing CVD did not show a statistically significant increase in risk associated with TTh. Overall quality of evidence was rated as low due to risk of bias and imprecision. Limitations of the study include lack of patient level data and ambiguous reporting on CV related events without predefined criteria. Funding sources were not evaluated; however, no apparent publication bias was noted.

Discussion

Final judgement on the safety and effectiveness of testosterone therapy is still unresolved in the eyes of many researchers and practitioners. The health benefits of TTh in hypogonadal men with testosterone levels <300 ng/dL (~ 10.5 nmol/L) have been well established in the literature and include increased muscle mass, increased bone density, decreased body fat, and improved sexual function¹⁹⁻²³. Conversely, the side effect profile for all modalities includes elevated hemoglobin/hematocrit and minimal increases in PSA without associated increased risk of prostate cancer²⁴⁻²⁶. Only a few studies suggest a detrimental effect on CV risk. One of the primary observational studies to suggest TTh increases CV adverse effects reported all case side

effects including minor self-reported episodes of syncope or edema that may or may not have resulted from therapy^{23,27}. In addition, another study did show a significant increase in CV events in patients treated at dosing levels well above recommended guidelines⁷. Overall comparisons of systematic reviews show no statistically significant combined association with increased CV risk or related events. Only one of the studies Xu et al¹³, indicated a statistically significant elevated risk but was later reevaluated and showed flawed statistical analysis based on the small number of reported CV events. That re-evaluation then supported the results of the other studies regarding CV-related events^{14,15}. Borst found that oral TTh may increase CV risk but this data was taken from only 4 studies and may not have provided enough information for appropriate analysis¹⁵. Albert & Morley's review discovered a potential elevated risk in >65-year-old men within the first 12 months of treatment; however, longer term use over 36 months did not raise risk. All studies stated deficiencies in reporting CV adverse effects by reviewed RCTs. The clear majority of the RCTs examined poorly defined parameters for what they considered CV-related events, skewing the distinction between related vs unrelated events. Meta-analyses presented in this review all sought to overcome this discrepancy by primarily looking at severe cardiac events as a separate study arm along with a composite analysis for overall risk.

Surprisingly, emerging data suggest that the CV *benefits* of TTh may outweigh the suspected risk associated with TTh especially in patients with associated cardiovascular comorbidities. Patients with metabolic syndrome and T2DM treated with TTh have shown marked improvements in CV risk factors such as central obesity, increased high-density lipoprotein (HDL), and insulin sensitivity²⁰. New evidence suggests heart failure patients could benefit from TTh. In a study by Webb et al, TTh resulted in increased left ventricular ejection fraction

(LVEF) without increasing LV hypertrophy or affecting cardiac volumes²⁸. It was also noted to reduce both central and peripheral arterial stiffness²⁸.

Clearly, with the number of sub-populations within the demographic of potential TTh patients regarding age and co-morbidities, more specific placebo-controlled trials need to be completed. Current evidence shows no direct, or at best a weak, association with CV risk and TTh and in some populations, may be protective. As such, TTh should be considered in individuals when appropriately diagnosed with low T, symptom improvement can be objectively monitored, and when careful planned follow up is in place.

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Appendix 1. – Forest Plots from meta-analysis.

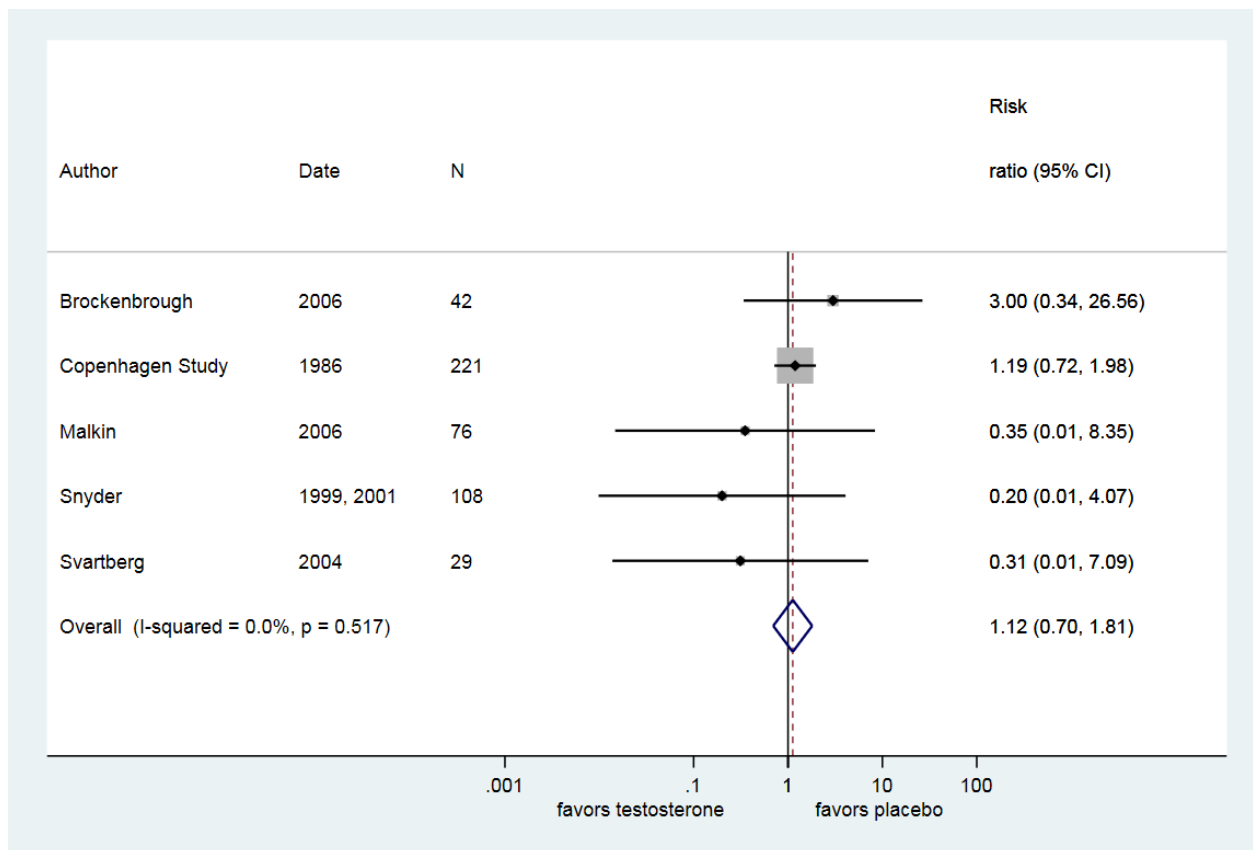


Figure 1. – Fernandez-Balsells et al combined CV-related mortality risk.

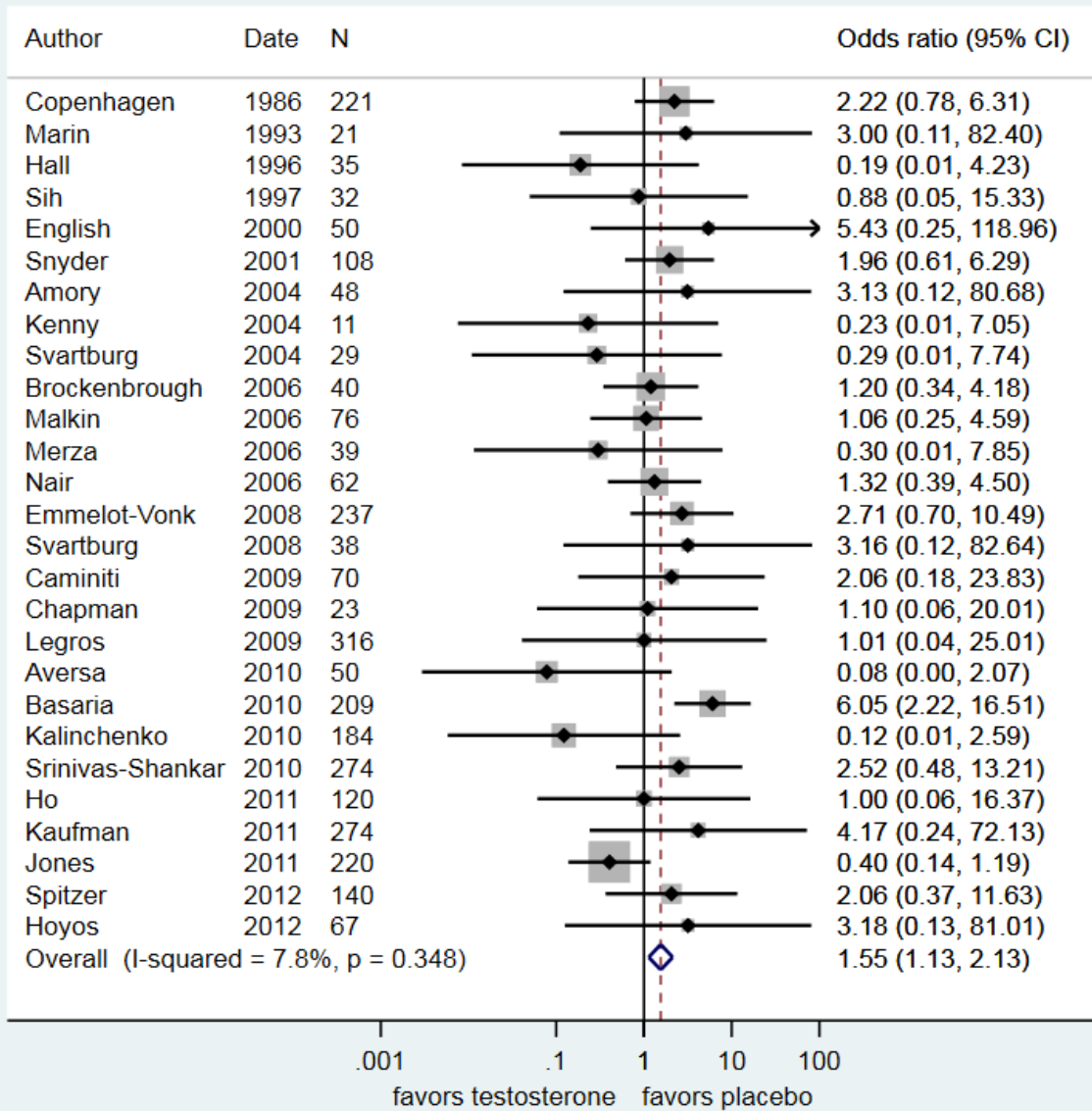


Figure 2. – Xu et al, Overall combined effect from RCTs on CV-related events.

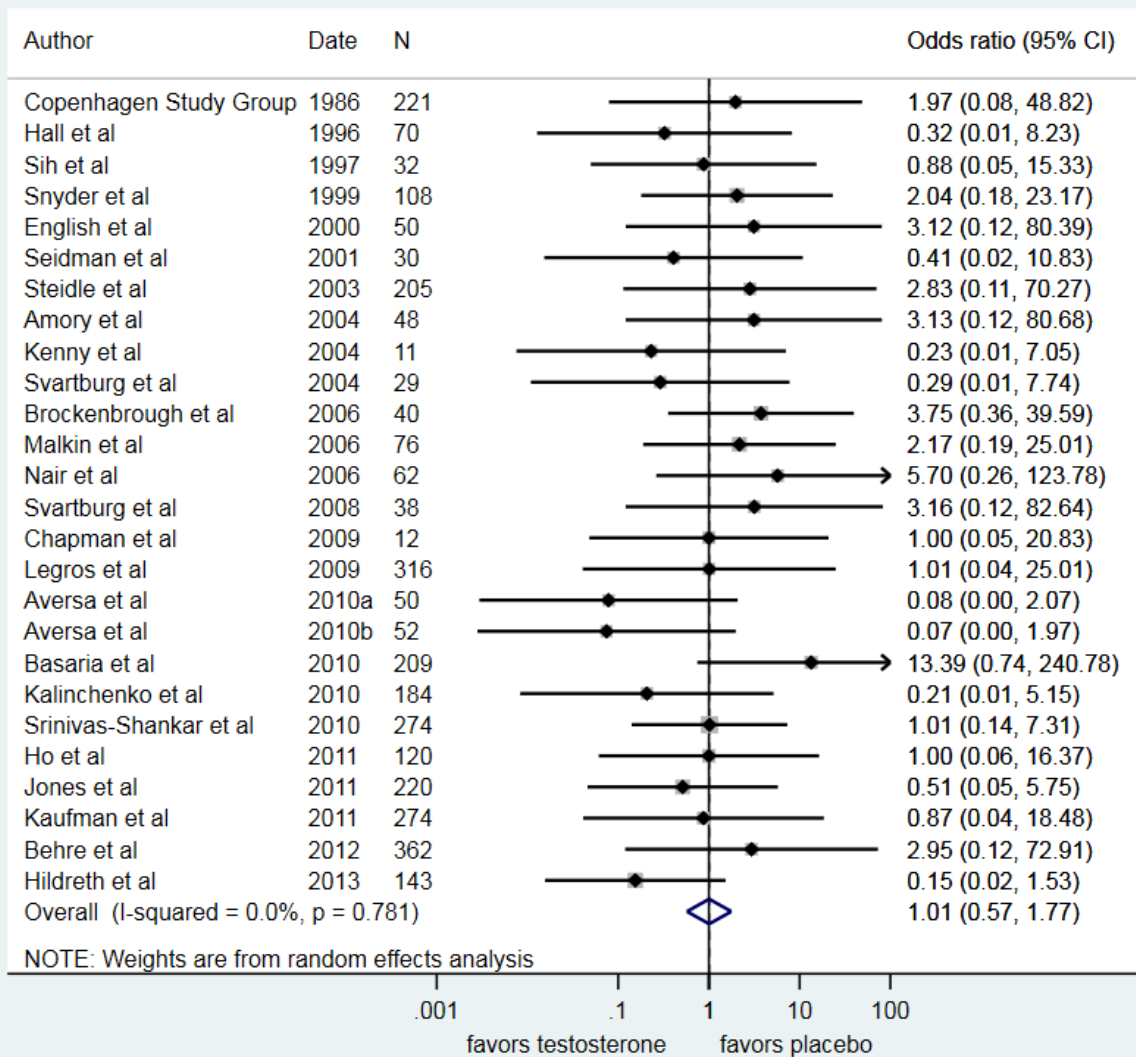


Figure 3. – Corona odds ratio for MACE in patients treated with TTh or placebo.

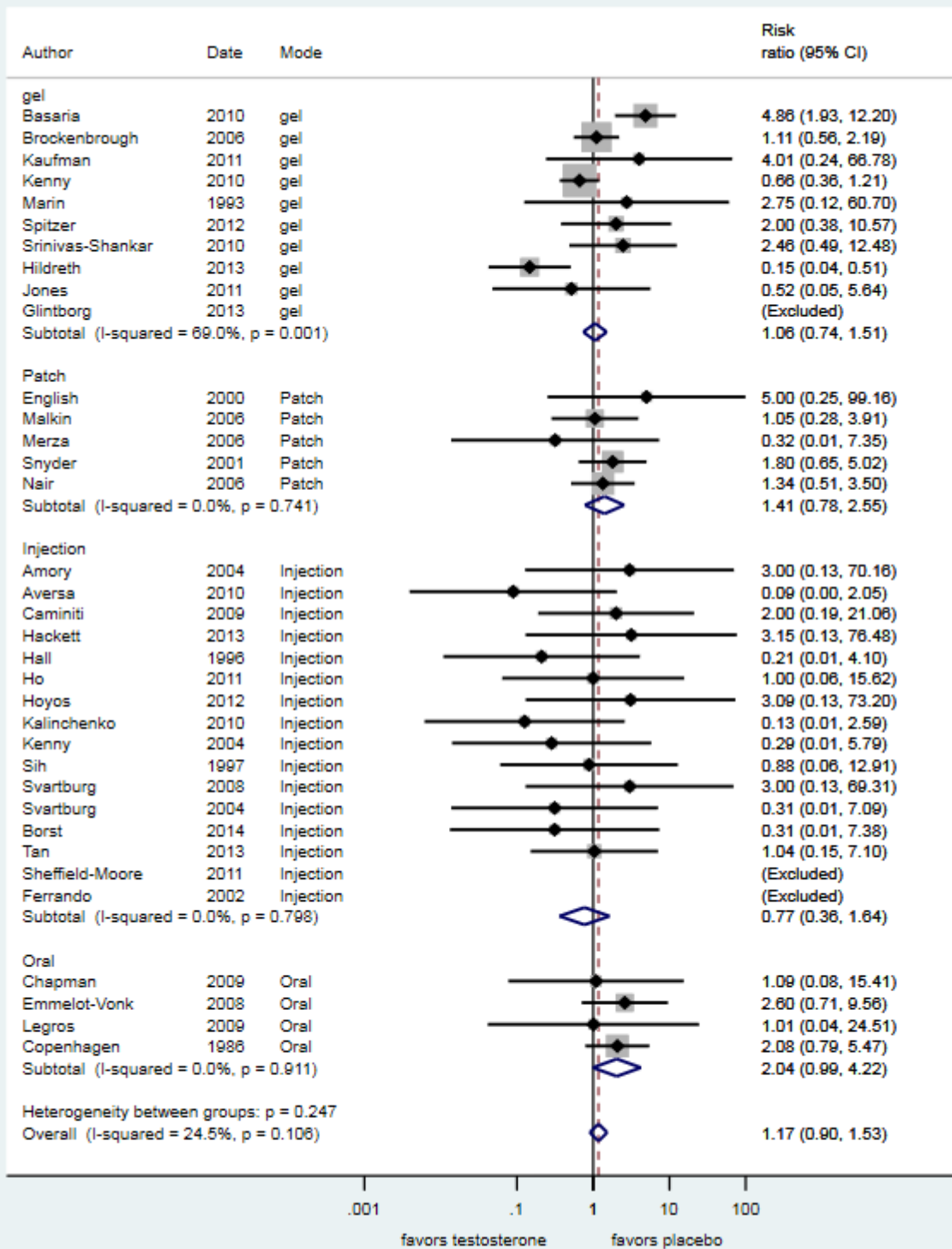


Figure 4. - Borst et al, combined CV-related risk from RCTs and individual CV-related risk by TTh treatment administration.

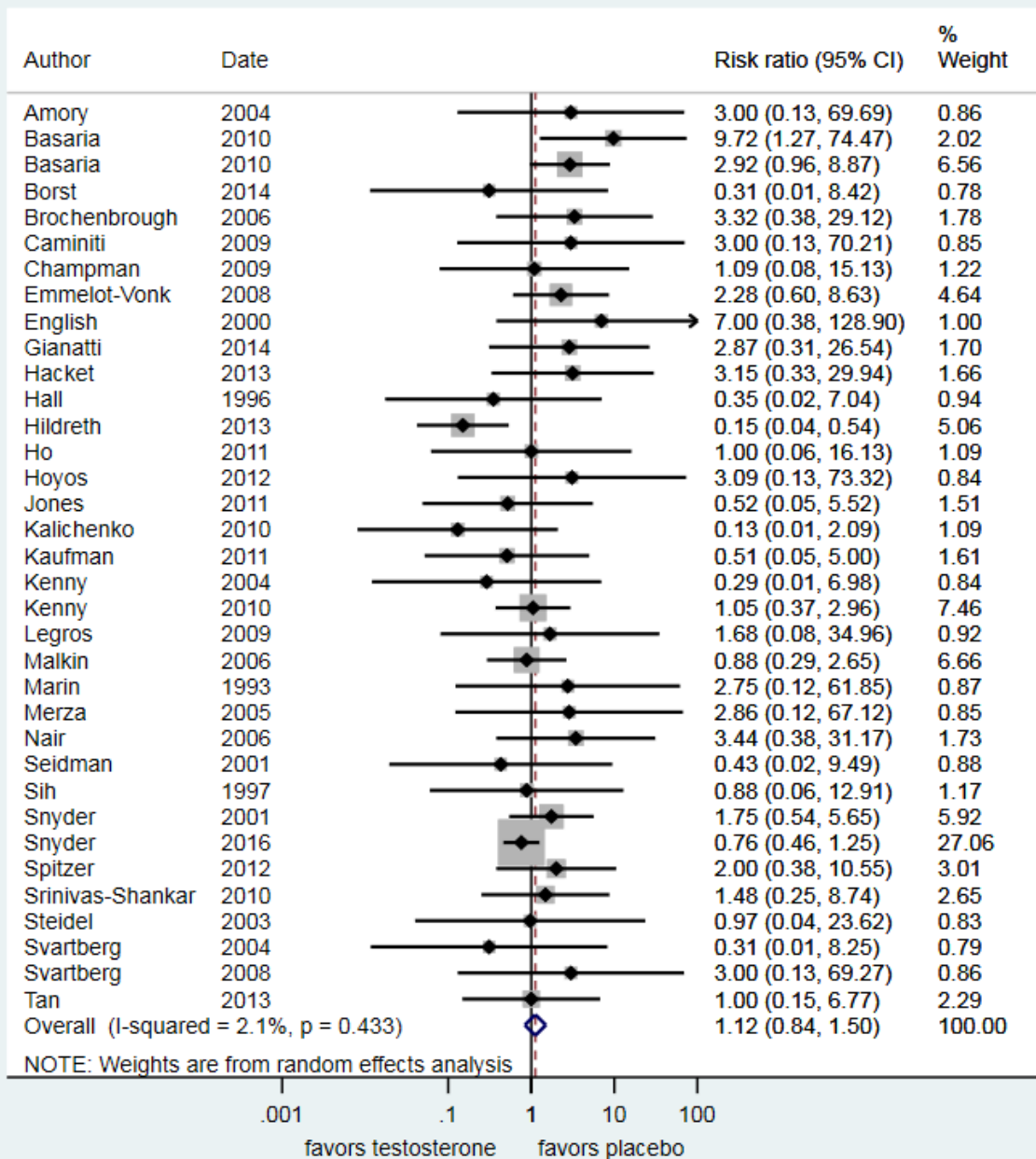


Figure 5. – Albert & Morley, overall relative risk of CV-related events.

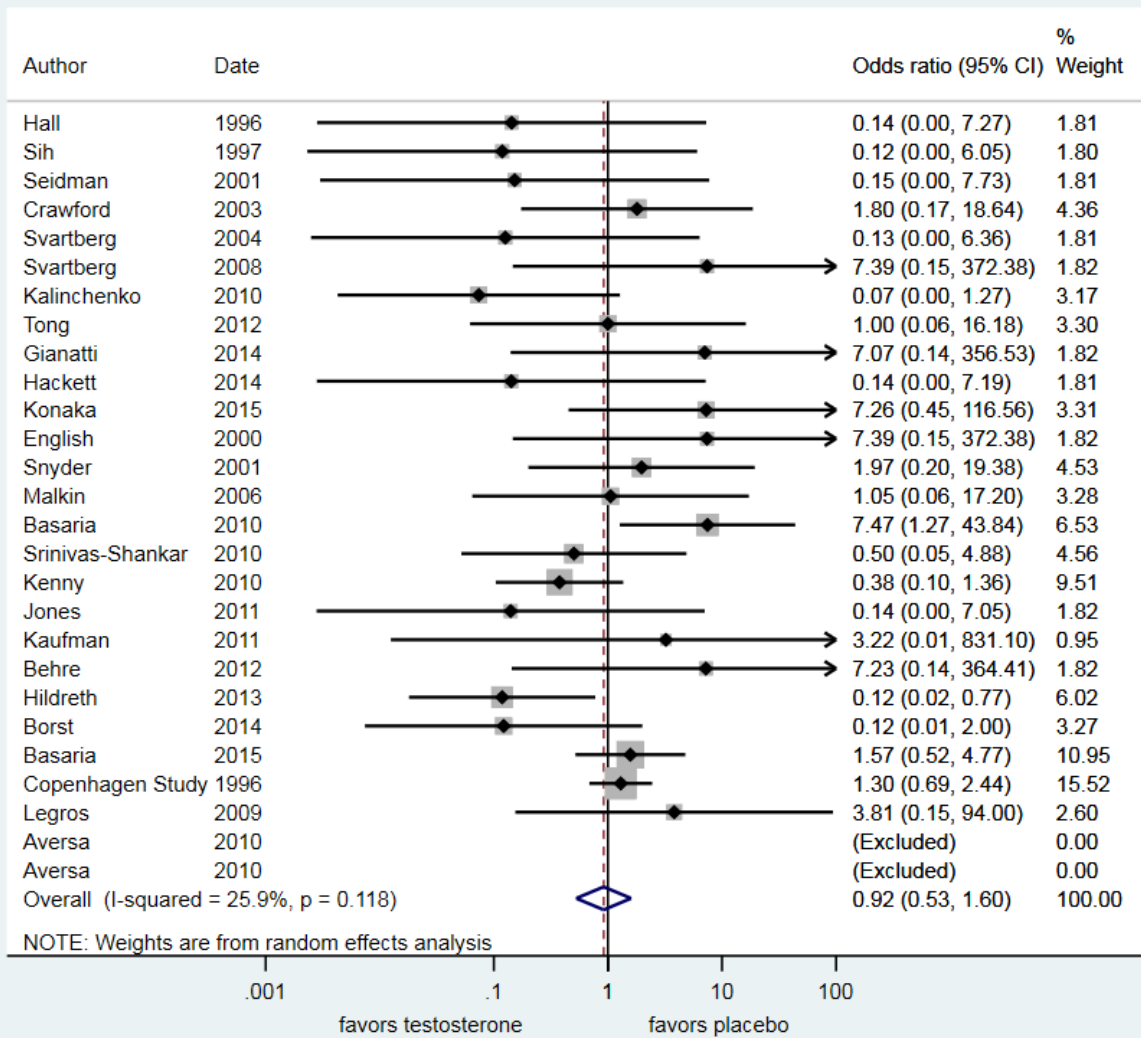


Figure 6. – Alexander et al, combined CV-related risk with TTh.