Testosterone Supplementation in Heart Failure: A Meta-Analysis

Toma et al: Testosterone in Heart Failure: A Meta-Analysis

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Journal Subject Codes: Other heart failure, Other Treatment
Abstract

Background—Low testosterone is an independent predictor of reduced exercise capacity and poor clinical outcomes in patients with heart failure (HF). We sought to determine if testosterone therapy improves exercise capacity in patients with stable chronic HF.

Methods and Results—We searched MEDLINE, EMBASE, Web of Science and Cochrane CENTRAL (1980 to 2010). Eligible studies included randomized trials reporting the effects of testosterone on exercise capacity in HF patients. Reviewers determined the methodological quality of studies and collected descriptive, quality, and outcome data. Four trials (n=198 patients, 84% male, mean age 67 years) were identified reporting the 6-minute walk test (6MWT, 2 RCT), incremental shuttle walk test (ISWT, 2 RCT) or peak VO2 (2 RCT) to assess exercise capacity after up to 52 weeks of treatment. Testosterone therapy was associated with a significant improvement in exercise capacity compared to placebo. The mean increase in the 6MWT, ISWT, and peak VO2 between the testosterone and placebo groups were 54.0 m (95% CI 43.0-65.0m), 46.7m (95% CI 12.6-80.9m), and 2.70 ml/kg/min (95% CI 2.68-2.72 ml/kg/min), respectively. Testosterone therapy was associated with a significant increase in exercise capacity as measured by units of pooled standard deviations (net effect 0.52 SD, 95% CI 0.10-0.94). No significant adverse cardiovascular events were noted.

Conclusions—Given the unmet clinical needs, testosterone appears to be a promising therapy to improve functional capacity in HF patients. Adequately powered RCT are required to assess the benefits of testosterone in this high-risk population assessing quality of life, clinical events and safety.

Key Words: heart failure, testosterone, androgen, meta-analysis
Despite advances in evidence-based pharmacological therapies, heart failure (HF) patients continue to exhibit significant morbidity and excess mortality at rates of up to 30% at one year.\textsuperscript{1,2} This high event rate, coupled with ongoing symptoms of fatigue, cardiac cachexia, and a metabolic shift towards catabolism has led to an intense search for therapies to further improve HF symptoms.

Age-related decline in testosterone levels in healthy men is associated with decreased muscle mass, muscle strength, and lower extremity strength.\textsuperscript{3-6} Testosterone and anabolic hormone deficiency are common and have been shown to be an independent risk markers for worse outcomes in heart failure patients of both sexes.\textsuperscript{7} Furthermore, reduced testosterone levels are an independent predictor of decreased peak VO\textsubscript{2} in men with HF.\textsuperscript{8,9} Jankowska et al. have shown that low testosterone levels and anabolic hormone depletion are common and are independent risk markers for decreased exercise capacity and poor prognosis in male heart failure patients.\textsuperscript{7,8,10} More recently, low testosterone levels have also been shown to be associated with decreased survival in male patients with coronary artery disease.\textsuperscript{9}

Treatment with supplemental testosterone results in favourable acute and chronic physiologic and biochemical changes in patients with cardiovascular disease. Testosterone supplementation in healthy men with testosterone deficiency have shown increased lean body mass and muscle mass without significant improvement in quality of life.\textsuperscript{11-14} Testosterone therapy has also been shown to increase hemoglobin and hematocrit and decrease HDL without causing significant change in fasting glucose, triglyceride or LDL levels or blood pressure in adult men without known cardiovascular disease.\textsuperscript{15} Furthermore, in patients with heart failure, intravenous testosterone administration acutely increases cardiac output and reduces peripheral
vascular resistance. Transdermal supplemental testosterone also causes coronary vasodilation, increased coronary blood flow, and improves angina threshold in patients with coronary artery disease.

Modestly-sized randomized, placebo-controlled trials have explored the effects of testosterone therapy on exercise capacity in HF patients using a variety of exercise-based endpoints. In this meta-analysis, we explore the effect of testosterone therapy, compared to placebo, on exercise capacity and metabolic indices in patients with HF and left ventricular systolic dysfunction.

Methods

Search Strategy

A broad search of the English-language literature for placebo-controlled RCT in patients with heart failure was performed using MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Web of Science and trials registries (clinicaltrials.org) databases, as well as hand searching of study bibliographies. Search terms used in the electronic search are provided in the appendix. Figure 1 summarizes the flowchart of article selection and inclusion.

Study Selection

Two investigators independently reviewed all titles and abstracts of citations to identify RCT evaluating the impact of testosterone supplementation in patients with heart failure on exercise capacity. Principally, this included an endpoint of a 6 minute-walk test or equivalent, or the peak oxygen consumption by cardiopulmonary exercise test. Trials that included heart failure patients of any age and sex were considered without restrictions on the route, dosage or frequency of testosterone supplementation.
Data Abstraction

Two independent investigators (MT and VV) extracted and tabulated data with standardized data-extraction forms. Discrepancies were resolved by consensus and by reference to the original reports. For each study, study population size (N), change in exercise capacity (6MWT or ISWT) with standard deviations, maximal oxygen consumption as measured by VO2, and route of testosterone administration was extracted. Quality assessment of all included studies was done using the 6 domains of the Cochrane's risk of bias tool. Studies were classified as having low, high, or unclear risk of bias.

Outcome Measures

The primary outcome measure was the weighted mean difference for the pooled estimates for exercise capacity (6MWT, ISWT, VO2) before and after intervention between the testosterone and placebo groups. Secondary outcomes were the weighted mean differences in pooled estimates for insulin resistance as measured by the homeostatic model assessment (HOMA-IR)23, fasting glucose, serum insulin, and serum free and total testosterone levels pre- and post-treatment as well as cardiovascular events.

Statistical analysis

As both the 6MWT and ISWT were used for assessments of exercise capacity in the studies to express the primary outcome, we calculated the standardized difference between the mean differences of the placebo and testosterone-treated groups in terms of baseline standard deviation change using Cohen’s D. To assess for consistency, peak VO2 was also normalized using Cohen’s D. Since no significant heterogeneity was detected across studies using I², we did not analyze the data using a meta-regression model. The inverse variance method was used as a weighting factor to combine the study results. In studies that used the same type of exercise or
metabolic measures, we determined the pooled mean differences of pre- and post-treatment measurements between testosterone and placebo. All p values were two-sided and p values of less than 0.05 were regarded as significant. All primary analyses were done using the rmeta package on R.2.12 (Vienna, Austria, 2011).

Results

Literature Search and Evaluation

From a total of 1,011 records that were identified, four published articles were included in the final quantitative synthesis (Figure 1). All four trials were randomized and double-blind. Randomization methods was not clear in one trial while allocation concealment was adequate in only two of the four trials. All four trials received funding from government agencies. A full list of search strategies, search results, and quality assessments for each included study are available in the appendix (Supplemental Table 1).

Studies included in the systematic review

Table 1 summarizes the characteristics of the 4 trials. Administration of testosterone differed between studies, with two studies using intramuscular (IM) injections (1 g of testosterone undeconate (Nebido) and Sustanon 100) and the other two using a transdermal patch (5 mg Androderm and 300 mcg Intrinsica). The primary outcome of change in exercise capacity was measured using the six-minute walk test (6MWT) as well as peak VO₂ in two trials, and the incremental shuttle walk test (ISWT) in the other two trials. None of the trials used baseline testosterone levels as an inclusion or exclusion criteria.

Overall, there were a total of 198 subjects; 166 (84%) were male, the mean age was 66.5 years (95%CI 60.0-76.8) and 71% had an ischemic etiology of HF. The mean LVEF was 28%
while 47%, 51%, and 2% had NYHA II, II, and IV symptoms, respectively. The mean baseline metabolic indices were as follows: 1.68 ng/ml (95%CI = 0.00-3.95) for total testosterone, 4.76 pg/ml (95%CI (0.00-14.90) for free testosterone, 1.33 mg/dl (95%CI 1.17-1.48) for creatinine, 112 mg/dl (95%CI 66.8-156.0) for fasting glucose, and 1.43 ng/ml (95%CI 0-2.89) for PSA. (Table 2) Medical therapy use was 90% for ACEi/ARB, 68% for beta-blockers, 48% for aldosterone antagonists, and 65% for diuretics.

Effect of testosterone supplementation on exercise capacity

The studies measuring the 6MWT, ISWT and peak VO₂ showed a net pooled mean increase of 54.0m (95%CI 43.0-65.0m; 16.7% increase), 46.7m (95%CI 12.6-80.9m; 15.9% increase), and 2.70ml/kg/min (95%CI 2.68-2.72ml/kg/min; 22.7% increase), respectively, for testosterone supplementation compared to placebo (Table 3). The 6MWT and ISWT demonstrated a pooled improvement of 0.52 SD (95%CI 0.10-0.94 SD) (Figure 2). In a sensitivity analysis excluding the one study enrolling only female patients, the effect size in the change in exercise capacity is 0.33 SD (95%CI 0.003-0.656). The peak VO₂ showed an increase of 1.23 SD (95%CI 0.14-2.32) in the two studies that examined this outcome. The increase in distance walked and peak VO₂ in the treatment groups was correlated with the increase in free or bioavailable testosterone. 19,20,22

Effect of testosterone supplementation on LVEF, symptoms, pharmacokinetics, and metabolic indices

LVEF did not change significantly in any of the studies. In two studies 20,22 NYHA class improved by one or more grades in 35% (20/57) of patients in the testosterone group vs. 9.8% (5/51) in the placebo group (OR = 4.9, 95%CI 1.6-16.8 p = 0.003). BNP did not change significantly in either of the two trials that reported this measure (-9.3 pg/ml vs +4.5 pg/ml, p = 0.063 and +43.3 pg/ml vs. +71.7 pg/ml, p = 0.65 for testosterone and placebo, respectively). 20,21
Two trials\textsuperscript{19, 22} reported baseline and end of treatment measurements for fasting insulin, HOMA-IR, and free testosterone, whereas 3 trials\textsuperscript{19, 20, 22} measured fasting glucose and total testosterone. The pooled net changes after 12-52 weeks of testosterone therapy were -0.62 mg/dl (95\%CI -0.85 to -0.38) for fasting glucose, -2.56 μU/ml (95\%CI -3.05 to -2.08) for insulin, -0.82 units (95\%CI -0.98 to -0.66) for HOMA-IR, +8.1 pg/ml (95\%CI -1.5 to 17.7) for free testosterone, and +1.65ng/ml (95\%CI 0.03 to 3.26) for total testosterone. Malkin et al. also reported a net increase in bio-available testosterone of 2.0 (SD 0.8) nmol/L.

Safety

None of the trials showed a significant change in PSA (0.10ng/ml, 95\%CI = 0.04, 0.16). Two trials showed a greater increase hematocrit in the testosterone group compared to placebo.\textsuperscript{20, 22} In the studies using topical testosterone, withdrawal of therapy due to due to skin reactions occurred in 19.3\% (11/57) in the testosterone group and 17.6\% (9/51) in the placebo group (OR = 1.12 95\% CI = 0.38-3.2; p = 0.8). In total, 46.3\% of patients developed skin reactions.

There were 13 clinical events that occurred overall. Only one death was reported in 84 patient-years of follow-up: this was a sudden cardiac death in the placebo group. Cardiovascular events (death/myocardial infarction/HF hospitalizations) were evenly distributed between the testosterone and placebo groups (7\% vs. 6\%, respectively; OR = 1.11, 95\%CI 0.36-3.41; p=1.00).

Discussion

This meta-analysis reveals that testosterone supplementation in heart failure patients with LV systolic dysfunction is associated with an improvement in exercise capacity by approximately 54 m using the 6 MWT. This degree of improvement does meet the definition of the minimal clinically important difference for the 6MWT (54 meters in a cohort of patients with chronic lung
disease \(^{25}\)) and is greater than that seen with other therapies currently used for morbidity and mortality reduction in patients with HF such as ACE inhibitors, beta-blockers and cardiac resynchronization therapy (CRT). \(^{26,27}\) Similarly, the increase in peak VO\(_2\) gained by testosterone treatment (2.7 ml/kg/min) is greater than the increase of 0.7 to 1.1 ml/kg/min observed in early CRT trials. \(^{27,28}\) Despite their modest sample size and differing routes of testosterone administration, all of these trials reported significant improvements in exercise capacity after 12-52 weeks of testosterone therapy. \(^{19-22}\) Further, there is an improvement in NYHA class as 35% of the testosterone group had an improvement of at least 1 NYHA class compared to ~10% in the placebo group. This absolute difference in improvement is similar to that gained by CRT compared to placebo (58% vs. 37%, respectively). \(^{27}\)

The improvement in exercise capacity in these trials occurred in the absence of improved myocardial structure or function as measured by echocardiography, as none of the trials in this meta-analysis showed improvement in LVEF. The mechanism for improvement in exercise capacity is complex and likely due to peripheral mechanisms. \(^{29}\) Testosterone has been shown to act as a peripheral vasodilator and acutely increases cardiac output. \(^{16}\) The improved oxygen delivery to skeletal muscles would secondarily delay transfer to anaerobic metabolism and depletion of high-energy phosphates. \(^{30}\) The increase in muscle mass associated with testosterone therapy in healthy men may similarly result in increased endurance and decreased muscle fatigability in HF patients. Other potential contributors to the functional improvement associated with testosterone therapy may include anti-inflammatory and immunosuppressive effects, a rise in hemoglobin \(^{15}\) and improved baroreceptor sensitivity \(^{22}\), which has the potential to improve muscle sympathetic nerve activity with concomitant increased muscle arteriole vasodilation and function. \(^{19}\)
Further, fasting glucose, fasting insulin and insulin resistance are all significantly improved after testosterone supplementation in this meta-analysis. Insulin resistance is common in HF patients, occurring in up to 40% of patients. This metabolic disturbance maybe related to low testosterone and can result in decreased glucose utilization by skeletal muscle, leading to muscle fatigue and wasting. Malkin has shown in a crossover study that insulin resistance as measured by HOMA-IR improves while lean body mass increases after testosterone therapy in men.

Testosterone supplementation has also proven to be beneficial in other chronic disease states like cancer, chronic renal disease, pulmonary disease, and HIV, with benefits noted in improved voluntary muscle strength, lean muscle mass, and reduced fat mass. None of these publications (44 studies, 1459 patients), however, showed a reduction (or increase) in clinical endpoints such as mortality or readmission.

Supra-therapeutic doses of anabolic steroids (which differ in chemical structure and properties from testosterone) are associated with reduced cardiac function and adverse outcomes. Despite the potential benefit of testosterone therapy, it also causes water and salt retention and concern has arisen recently based on the Testosterone in Older Men with Mobility Limitations (TOM) trial, which was halted early due to a significantly higher risk of cardiovascular events in the testosterone treated group. However, patients with symptomatic heart failure were excluded from the TOM trial and there were only 28 cardiovascular events in the trial. Further, this trial used higher doses of testosterone and further allowed for up-titration based on serum testosterone levels and it is uncertain if this contributed to the small excess of cardiovascular events. In addition, prior meta-analyses of 6 RCT enrolling patients without known cardiovascular disease did not detect significant changes in the rates of death, myocardial
infarction, revascularization procedures, or cardiac arrhythmias in those exposed to testosterone compared to placebo (although there were only 21 events in 308 patients). 15, 41

Our meta-analysis showed that there were no safety concerns reported in any of the trials, although data was limited given the small sample sizes and short durations of follow-up. Despite the concern in regards to the long-term risk of prostate cancer, currently available data does not support a link between testosterone replacement therapy and prostate cancer. 42-47 Although there were no significant changes in PSA in any individual trial, the pooled estimates indicate a small, albeit significant, increase in PSA. Most of the trials using testosterone in HF were of short duration and follow-up and long-term surveillance in larger numbers of patients will be required to evaluate its potential therapeutic role and risk profile.

Limitations

The trials included in this study followed patients for variable lengths of time (12-52 weeks), however we were able to combine their results in this meta-analysis. The two trials following patients for greater than 12 weeks have shown that the beneficial effects of testosterone occur early and are sustained for up to 12-months. Also, the 4 studies included utilized two different routes of administration for testosterone: IM and transdermal. However, the standardized improvement in terms of baseline SD was consistent across the 4 studies regardless of route of administration. Finally, although the majority of patients enrolled in testosterone trials are male, we believe that these results are likely generalizable to female patients based on the currently proposed mechanisms of action and the consistent results seen in the one study that included 32 female HF patients. 22
Conclusions

In patients with moderate to severe HF, testosterone supplementation improves exercise capacity and metabolic indices. Testosterone is a promising therapy to improve exercise capacity in heart failure patients. Adequately powered RCT are now required to assess the benefits of testosterone in this high-risk population assessing quality of life, clinical events and safety.

Sources of Funding

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Disclosures

None.

References

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29. Armstrong PW, Ezekowitz JA. Testosterone therapy in women with heart failure "why can't a woman be more like a man?". *Journal of the American College of Cardiology*. 2010;56:1317-1319.


Table 1. Summary of Trial Characteristics (Evidence Table)

<table>
<thead>
<tr>
<th>Author, year</th>
<th>N</th>
<th>HF status</th>
<th>Sex</th>
<th>Major Inclusion criteria</th>
<th>Major Exclusion criteria</th>
<th>Testosterone</th>
<th>Trial Duration</th>
<th>LVEF Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pugh 2004²¹</td>
<td>20</td>
<td>Stable HF (100%)</td>
<td>Male</td>
<td>HF for at least 6 months, at least moderate LV dysfunction by echo, and reduced exercise tolerance</td>
<td>malignancy or debilitating disease, high PSA</td>
<td>Sustanon 100mg IM q2 weeks for 12 weeks</td>
<td>12 weeks</td>
<td>35±8%</td>
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<tr>
<td>Malkin 2006²⁰</td>
<td>76</td>
<td>Stable HF (100%)</td>
<td>Male</td>
<td>Stable CHF ≥6 months, Impaired Exercise tolerance, at least mod LV dysfunction by echo</td>
<td>High PSA, use of sex hormone therapy</td>
<td>Androderm 5mg q24h</td>
<td>12 months</td>
<td>32.5±11%</td>
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<tr>
<td>Caminiti 2009¹⁹</td>
<td>70</td>
<td>Stable HF (100%)</td>
<td>Male</td>
<td>LVEF&lt;40%, NYHA 2 or 3, No hospital admission in previous 3 months</td>
<td>UA, Recent MI</td>
<td>Long acting T undecanoate (Nebido) IM at 0, 6, 12 weeks</td>
<td>12 weeks</td>
<td>31.8±7%</td>
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<tr>
<td>Iellamo 2010²²</td>
<td>32</td>
<td>Stable HF (100%)</td>
<td>Female</td>
<td>LVEF&lt;40%, NYHA 3, no hospitalization in previous 3 months</td>
<td>UA, recent MI, malignancy, HRT</td>
<td>Transdermal T</td>
<td>6 months</td>
<td>28±1%</td>
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Legend: UA: unstable angina, MI: myocardial infarction, PSA: prostate specific antigen, HRT: hormone replacement therapy
Table 2. Baseline characteristics of patients by individual trial

<table>
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<tr>
<th>Study</th>
<th>n</th>
<th>Age, years, mean</th>
<th>Male (%)</th>
<th>Ischemic etiology (%)</th>
<th>Mean LVEF (%)</th>
<th>NYHA Class, n</th>
<th>Total T (ng/ml)</th>
<th>Free T (pg/ml)</th>
<th>Creatinine (mg/dl)</th>
<th>Fasting insulin (mcg/mL)</th>
<th>Fasting glucose (mg/dl)</th>
<th>TC (mg/dl)</th>
<th>HDL (mg/dl)</th>
<th>TG (mg/dl)</th>
<th>PSA (ng/mL)</th>
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<td>Treated</td>
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<td>63.1</td>
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<td>Iellamo 2010</td>
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* This value reflects bioavailable testosterone.

Legend: EF: ejection fraction; NYHA: New York Heart Association; T: testosterone; TC: total cholesterol; HDL: high density lipoprotein; TG: triglycerides; PSA prostate-specific antigen; NR: not reported
Table 3. Raw outcomes for change in exercise capacity by individual trial

<table>
<thead>
<tr>
<th>Study</th>
<th>Treated (N)</th>
<th>Placebo (N)</th>
<th>Measure of exercise capacity</th>
<th>Exercise capacity Before, m (SD)</th>
<th>Exercise capacity After, m (SD)</th>
<th>Mean change in exercise capacity, m (SD)</th>
<th>Cohen’s d (SE)</th>
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<tbody>
<tr>
<td>Pugh</td>
<td>10</td>
<td>10</td>
<td>ISWT</td>
<td>328 (174)</td>
<td>419 (200)</td>
<td>91 (19.7)</td>
<td>0.42 (0.26)</td>
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<td>ISWT</td>
<td>280 (162.9) NR</td>
<td>298 NR</td>
<td>20 (8)</td>
<td>0.19 (0.25)</td>
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<tr>
<td>Caminiti</td>
<td>31</td>
<td>33</td>
<td>6MWT</td>
<td>386.6 (121)</td>
<td>472.8 (138.4)</td>
<td>86.2 (14.5)</td>
<td>0.47 (0.45)</td>
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<tr>
<td>Iellamo</td>
<td>20</td>
<td>12</td>
<td>6MWT</td>
<td>260.6 (52)</td>
<td>357.2 (43)</td>
<td>96.6 (14.5)</td>
<td>1.26 (0.40)</td>
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Legend: 6MWT: 6-minute walk test; ISWT: incremental shuttle walk test; NR: not reported.

Values are means (standard deviations) unless otherwise stated.
Figure Legends

Figure 1. Search strategy.

Figure 2. Forest Plot of exercise capacity in all studies, normalized using standard deviation.

Legend: This forest plot shows that testosterone therapy resulted in a net-pooled improvement in exercise capacity of 0.52 SD, 95% CI 0.10-0.94.
1010 records identified through database search
1 record identified through hand search

1011 total records identified
67 duplicate records removed

944 records screened

918 records excluded based on unrelated title
7 full-text articles excluded
-no exercise capacity measured
-review articles
-no Testosterone supplementation given

15 abstracts excluded
-no exercise capacity measured
-no Testosterone supplementation given
-no absolute \( \Delta \) in walking dist. given
-abstracts of published articles

10 full-text articles and 16 abstracts assessed for eligibility (Total of 26)

4 studies included in qualitative synthesis

4 studies included in quantitative synthesis (Meta-Analysis)
Testosterone Supplementation in Heart Failure: A Meta-Analysis
Mustafa Toma, Finlay A. McAlister, Erin E. Coglianese, Venketesan Vidi, Samip Vasaiwala, Jeffrey A. Bakal, Paul W. Armstrong and Justin A. Ezekowitz

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Data Supplement (unedited) at:
http://circheartfailure.ahajournals.org/content/suppl/2012/04/17/CIRCHEARTFAILURE.111.965632.DC1

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Table 1: Cochrane Risk of Bias Assessment

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<th>Pugh</th>
<th>Malkin</th>
<th>Caminiti</th>
<th>Iellamo</th>
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<td>Unclear</td>
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<td>Blinding</td>
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<tr>
<td>Incomplete outcome data</td>
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<td>Selective outcome reporting</td>
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<td>Other potential threats</td>
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