

Testosterone Supplementation in Heart Failure

A Meta-Analysis

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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 whether testosterone therapy improves exercise capacity in patients with stable chronic HF.

Methods and Results—We searched Medline, Embase, Web of Science, and Cochrane Central Register of Controlled Trials (1980–2010). Eligible studies included randomized controlled trials (RCTs) reporting the effects of testosterone on exercise capacity in patients with HF. Reviewers determined the methodological quality of studies and collected descriptive, quality, and outcome data. Four trials (n=198; men, 84%; mean age, 67 years) were identified that reported the 6-minute walk test (2 RCTs), incremental shuttle walk test (2 RCTs), or peak oxygen consumption (2 RCTs) to assess exercise capacity after up to 52 weeks of treatment. Testosterone therapy was associated with a significant improvement in exercise capacity compared with placebo. The mean increase in the 6-minute walk test, incremental shuttle walk test, and peak oxygen consumption between the testosterone and placebo groups was 54.0 m (95% CI, 43.0–65.0 m), 46.7 m (95% CI, 12.6–80.9 m), and 2.70 mL/kg per min (95% CI, 2.68–2.72 mL/kg per min), respectively. Testosterone therapy was associated with a significant increase in exercise capacity as measured by units of pooled SDs (net effect, 0.52 SD; 95% CI, 0.10–0.94 SD). 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 patients with HF. Adequately powered RCTs are required to assess the benefits of testosterone in this high-risk population with regard to quality of life, clinical events, and safety. (*Circ Heart Fail.* 2012;5:315-321.)

Key Words: heart failure ■ testosterone ■ androgens ■ meta-analysis

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

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Age-related decline in testosterone levels in healthy men is associated with decreased muscle mass, muscle strength, and lower-extremity strength.^{3–6} Testosterone and anabolic hormone deficiency are common and have been shown to be an independent risk marker for worse outcomes in patients with HF of both sexes.⁷ Furthermore, reduced testosterone levels are an independent predictor of decreased peak oxygen consumption ($\dot{V}O_2$) in men with HF.^{8,9} Jankowska et al^{7,8,10}

showed that low testosterone levels and anabolic hormone depletion are common and are independent risk markers for decreased exercise capacity and poor prognosis in male patients with HF. More recently, low testosterone levels were also shown to be associated with decreased survival in male patients with coronary artery disease.⁹

Treatment with supplemental testosterone results in favorable acute and chronic physiological 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.^{11–14} Testosterone therapy has also been shown to increase hemoglobin and hematocrit levels and to decrease high-density lipoprotein level without causing a significant change in fasting glucose, triglyceride, or low-density lipoprotein levels or blood pressure in adult men without known cardiovascular

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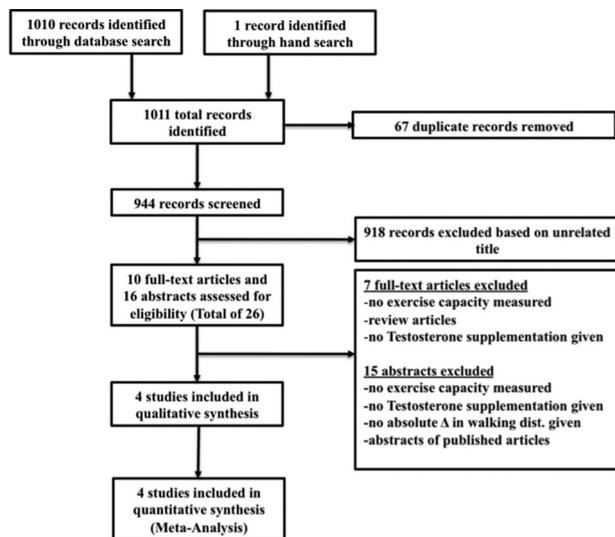


Figure 1. Search strategy.

disease.¹⁵ Furthermore, in patients with HF, intravenous testosterone administration acutely increases cardiac output and reduces peripheral vascular resistance.¹⁶ Transdermal supplemental testosterone also causes coronary vasodilation and increased coronary blood flow and improves angina threshold in patients with coronary artery disease.^{17,18}

Modestly sized randomized, placebo-controlled trials have explored the effects of testosterone therapy on exercise capacity in patients with HF, using a variety of exercise-based end points.^{19–22} In this meta-analysis, we explore the effect of testosterone therapy compared with 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 randomized controlled trials in patients with HF was performed using Medline, Embase, Cochrane Central Register of Controlled Trials, Web of Science, and trial registry (eg, Clinical-Trials.org) databases as well as a hand search of study bibliographies. Terms used in the electronic search are provided in the online-only Data Supplement. Figure 1 shows a flowchart of article selection and inclusion.

Study Selection

Two investigators independently reviewed all titles and abstracts of citations to identify randomized controlled trials evaluating the impact on exercise capacity of testosterone supplementation in patients with HF. Principally, this included an end point of a 6 minute-walk test (6MWT) or equivalent or the peak $\dot{V}O_2$ by cardiopulmonary exercise test. Trials that included patients with HF of any age and sex were considered without restrictions on the route, dose, or frequency of testosterone supplementation.

Data Abstraction

Two independent investigators (M.T. and V.V.) 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, changes in exercise capacity (6MWT or incremental shuttle walk test [ISWT]) with SDs, maximal $\dot{V}O_2$, and route of testosterone administration were extracted. Quality assessment of all included studies was done using

the 6 domains of the Cochrane 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, $\dot{V}O_2$) before and after intervention between the testosterone and the 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, serum free and total testosterone levels pretreatment and posttreatment, and cardiovascular events.

Statistical Analysis

Because both the 6MWT and the 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 SD change using Cohen D. To assess for consistency, peak $\dot{V}O_2$ was also normalized using Cohen D. Because no significant heterogeneity was detected across studies using I^2 , 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 pretreatment and post-treatment measurements between testosterone and placebo. All P values were 2 sided, and $P < 0.05$ was regarded as significant. All primary analyses were done using the *rmeta* package on R version 2.12.²⁴

Results

Literature Search and Evaluation

From a total of 1011 records identified, 4 published articles were included in the final quantitative synthesis (Figure 1). All 4 trials were randomized and double blind. The randomization method was not clear in 1 trial,²¹ whereas allocation concealment was adequate in only 2 of the 4 trials.^{19,22} All 4 trials received funding from government agencies. A full list of search strategies, search results, and quality assessments for each included study are available in online-only Data Supplement Table I.

Studies Included in the Systematic Review

Table 1 summarizes the characteristics of the 4 trials. Administration of testosterone differed among studies, with 2 using intramuscular injections (1 g testosterone undecanoate [Nebido¹⁹ and Sustanon 100²¹]) and the other 2 using a transdermal patch (5 mg Androderm²⁰ and 300 μ g Intrinsa²²). The primary outcome of change in exercise capacity was measured using the 6MWT and peak $\dot{V}O_2$ in 2 trials^{19,22} and the ISWT in the other 2.^{20,21} None of the trials used baseline testosterone level as an inclusion or exclusion criterion.

Overall, there were a total of 198 subjects (166 [84%] men; mean age, 66.5 years; 95% CI, 60.0–76.8 years; ischemic etiology of HF, 71%). The mean left ventricular ejection fraction was 28%, whereas 47%, 51%, and 2% had New York Heart Association functional class II, III, and IV symptoms, respectively. The mean baseline metabolic indices were as follows: total testosterone, 1.68 ng/mL (95% CI, 0.00–3.95 ng/mL); free testosterone, 4.76 pg/mL (95% CI, 0.00–14.90 pg/mL); creatinine level, 1.33 mg/dL (95% CI, 1.17–1.48 mg/dL); fasting glucose, 112 mg/dL (95% CI, 66.8–156.0 mg/dL); and prostate-specific antigen, 1.43 ng/mL (95% CI,

Table 1. Summary of Trial Characteristics (Evidence Table)

| Author, Year | N | HF Status | Sex (%) | Major Inclusion Criteria | Major Exclusion Criteria | Testosterone | Trial Duration | LVEF, %* |
|------------------------------------|----|-----------|--------------|--|--|---|----------------|----------|
| Pugh et al, 2004 ²¹ | 20 | Stable HF | Male (100) | HF for at least 6 mo, at least moderate LV dysfunction by echocardiography, reduced exercise tolerance | Malignancy or debilitating disease, high PSA | Sustanon 100 mg IM every 2 wk for 12 wk | 12 wk | 35±8 |
| Malkin et al, 2006 ²⁰ | 76 | Stable HF | Male (100) | Stable CHF ≥6 mo, impaired exercise tolerance, at least moderate LV dysfunction by echocardiography | High PSA, use of sex hormone therapy | Androderm 5 mg every 24 h | 12 mo | 32.5±11 |
| Caminiti et al, 2009 ¹⁹ | 70 | Stable HF | Male (100) | LVEF <40%, NYHA functional class II or III, no hospital admission in previous 3 mo | UA, recent MI | Long-acting testosterone undecanoate (Nebido) IM at 0, 6, 12 wk | 12 wk | 31.8±7 |
| Iellamo et al, 2010 ²² | 32 | Stable HF | Female (100) | LVEF <40%, NYHA functional class III, no hospitalization in previous 3 mo | UA, recent MI, malignancy, HRT | Transdermal testosterone | 6 mo | 28±1 |

HF indicates heart failure; LVEF, left ventricular ejection fraction; LV, left ventricular; PSA, prostate-specific antigen; CHF, congestive heart failure; NYHA, New York Heart Association; UA, unstable angina; MI, myocardial infarction; HRT, hormone replacement therapy.
 *Data are presented as mean±SD.

0–2.89 ng/mL) (Table 2). Medical therapy use was 90% for angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, 68% for β-blockers, 48% for aldosterone antagonists, and 65% for diuretics.

Effect of Testosterone Supplementation on Exercise Capacity

The studies measuring the 6MWT, ISWT, and peak $\dot{V}O_2$ showed a net pooled mean increase of 54.0 m (95% CI,

Table 2. Baseline Characteristics of Patients by Individual Trial

| Author, Year | n | Mean Age, y | Male, % | Ischemic Etiology, % | Mean LVEF, % | NYHA Class-n | Total T, ng/mL | Free T, pg/mL | Creatinine, mg/dL | Fasting Insulin, μg/mL | Fasting Glucose, mg/dL | TC, mg/dL | HDL, mg/dL | TG, mg/dL | PSA, ng/mL |
|------------------------------------|----|-------------|---------|----------------------|--------------|----------------|----------------|---------------|-------------------|------------------------|------------------------|-----------|------------|-----------|------------|
| Pugh et al, 2004 ²¹ | | | | | | | | | | | | | | | |
| Treated | 10 | 62 | 100 | NR | 35 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| Placebo | 10 | 62 | 100 | NR | 35 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| Malkin et al, 2006 ²⁰ | | | | | | | | | | | | | | | |
| Treated | 37 | 63.1 | 100 | 51 | 33.8 | II-21, III, IV | 4.0 | 4.7 nmol/L* | 1.3 | NR | 106.2 | NR | NR | NR | 1.7 |
| Placebo | 39 | 64.9 | 100 | 56 | 33.1 | II-24, III, IV | 3.5 | 4.6 nmol/L* | 1.2 | NR | 113.4 | NR | NR | NR | 1.5 |
| Caminiti et al, 2009 ¹⁹ | | | | | | | | | | | | | | | |
| Treated | 35 | 71 | 100 | 74 | 31.5 | II-18, III-17 | 2.3 | 11.3 | 1.4 | 10.4 | 114.8 | 142.5 | 36.3 | 131.2 | 1.4 |
| Placebo | 35 | 69 | 100 | 80 | 33.8 | II-20, III-15 | 2.1 | 12.1 | 1.4 | 11.0 | 111.0 | 147.3 | 37.0 | 138.6 | 1.3 |
| Iellamo et al, 2010 ²² | | | | | | | | | | | | | | | |
| Treated | 20 | 68.2 | 0 | 100 | 32.3 | III-20 | 0.4 | 0.95 | 1.3 | 12.6 | 109.3 | 138.5 | 31.3 | 128.2 | NA |
| Placebo | 12 | 69.1 | 0 | 100 | 31.8 | III-12 | 0.4 | 0.93 | 1.3 | 11.8 | 114.1 | 140.5 | 37.0 | 129.1 | NA |

LVEF indicates left ventricular ejection fraction; NYHA, New York Hear Association; T, testosterone; TC, total cholesterol; HDL, high-density lipoprotein; TG, triglycerides; PSA, prostate-specific antigen; NR, not reported; NA, not available.

*This value reflects bioavailable testosterone.

Table 3. Raw Outcomes for Change in Exercise Capacity by Individual Trial

| Author, Year | No. Treated | No. Placebo | Measure of Exercise Capacity | Exercise Capacity Testosterone Group | | Exercise Capacity Placebo Group | | Change in Exercise Capacity in Testosterone Group, m* | Change in Exercise Capacity in Placebo Group, m* | Difference of Mean Change, m† | Cohen D‡ |
|------------------------------------|-------------|-------------|------------------------------|--------------------------------------|-------------|---------------------------------|-----------|---|--|-------------------------------|-----------|
| | | | | Before, m* | After, m* | Before, m* | After, m* | | | | |
| Pugh et al, 2004 ²¹ | 10 | 10 | ISWT | 328±174 | 419±200 | 314±92 | 340±101 | 91±19.7 | 26±15.2 | 65±7.87 | 0.42±0.26 |
| Malkin et al, 2006 ²⁰ | 29 | 34 | ISWT | 280±162.9 | NR | 298±158.9 | NR | 20±8 | -10±7 | 30±1.91 | 0.19±0.25 |
| Caminiti et al, 2009 ¹⁹ | 31 | 33 | 6MWT | 386.6±121 | 472.8±138.4 | 390.9±107.4 | 428.2±112 | 86.2±14.5 | 37.3±8.7 | 48.9±3.01 | 0.47±0.45 |
| Iellamo et al, 2010 ²² | 20 | 12 | 6MWT | 260.6±52 | 357.2±43 | 254.9±39 | 291.3±22 | 96.6±14.5 | 36.4±11.9 | 60.2±4.72 | 1.26±0.40 |

ISWT indicates incremental shuttle walk test; NR, not reported; 6MWT, 6-minute walk test.

*Data are presented as mean±SD.

†Data are presented as mean±SE.

43.0–65.0 m; 16.7% increase), 46.7 m (95% CI, 12.6–80.9 m; 15.9% increase), and 2.70 mL/kg per min (95% CI, 2.68–2.72 mL/kg per min; 22.7% increase), respectively, for testosterone supplementation compared with 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 1 study enrolling only female patients, the effect size in the change in exercise capacity was 0.33 SD (95% CI, 0.003–0.656 SD). The peak $\dot{V}O_2$ showed an increase of 1.23 SD (95% CI, 0.14–2.32 SD) in the 2 studies that examined this outcome. The increase in distance walked and peak $\dot{V}O_2$ in the treatment groups was correlated with the increase in free or bioavailable testosterone.^{19,20,22}

Effect of Testosterone Supplementation on Left Ventricular Ejection Fraction, Symptoms, Pharmacokinetics, and Metabolic Indices

Left ventricular ejection fraction did not change significantly in any of the studies. In 2 studies^{20,22} New York Heart

Association functional class improved by ≥ 1 grade in 35% (20/57) of patients in the testosterone group versus 9.8% (5/51) in the placebo group (odds ratio, 4.9; 95% CI, 1.6–16.8; $P=0.003$). Brain natriuretic peptide levels did not change significantly in either of the 2 trials that reported this measure^{20,21} (testosterone, -9.3 versus +4.5 pg/mL; $P=0.063$; placebo, +43.3 versus +71.7 pg/mL; $P=0.65$).

Two trials^{19,22} reported baseline and end-of-treatment measurements for fasting insulin, HOMA-IR, and free testosterone, whereas 3 trials^{19,20,22} measured fasting glucose and total testosterone. The pooled net changes after 12 to 52 weeks of testosterone therapy were -0.62 mg/dL (95% CI, -0.85 to -0.38 mg/dL) for fasting glucose, -2.56 μ U/mL (95% CI, -3.05 to -2.08 μ U/mL) for insulin, -0.82 U (95% CI, -0.98 to -0.66 U) for HOMA-IR, +8.1 pg/mL (95% CI, -1.5 to +17.7 U) for free testosterone, and +1.65 ng/mL (95% CI, +0.03 to +3.26 ng/mL) for total testosterone. Malkin et al²⁰ also reported a net increase in bioavailable testosterone of 2.0±0.8 nmol/L.

Safety

None of the trials showed a significant change in prostate-specific antigen (0.10 ng/mL; 95% CI, 0.04–0.16 ng/mL). Two trials showed a greater increase hematocrit level in the testosterone group than in the placebo group.^{20,22} In the studies using topical testosterone, withdrawal of therapy because of skin reactions occurred in 19.3% (11/57) in the testosterone group and 17.6% (9/51) in the placebo group (odds ratio, 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 1 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 hospitalization) were evenly distributed between the testosterone and the placebo groups (7% versus 6%, respectively; odds ratio, 1.11; 95% CI, 0.36–3.41; $P=1.00$).

Discussion

This meta-analysis reveals that testosterone supplementation in patients with HF with left ventricular systolic dysfunction is associated with an improvement in exercise capacity by ≈ 54 m using the 6MWT. This degree of improvement does

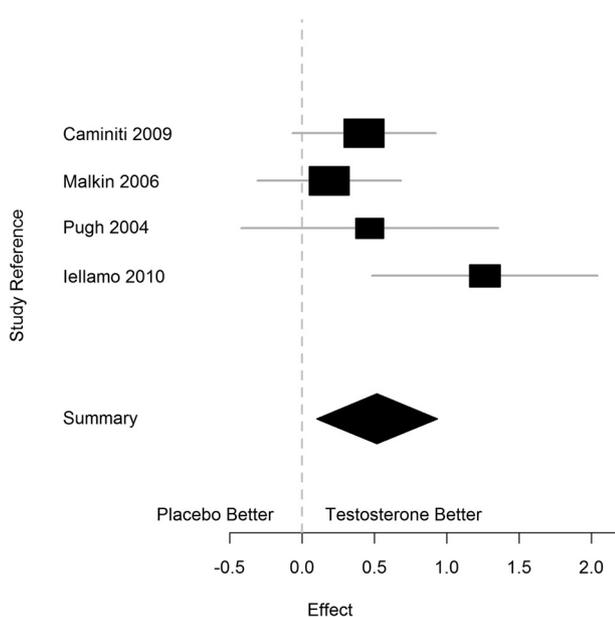


Figure 2. Forest plot of exercise capacity in all studies, normalized using SD. This forest plot shows that testosterone therapy resulted in a net pooled improvement in exercise capacity of 0.52 SD (95% CI, 0.10–0.94 SD).

meet the definition of the minimal clinically important difference for the 6MWT (54 m in a cohort of patients with chronic lung disease²⁵) and is greater than that seen with other therapies currently used for morbidity and mortality reduction in patients with HF, such as angiotensin-converting enzyme inhibitors, β -blockers, and cardiac resynchronization therapy.^{26,27} Similarly, the increase in peak $\dot{V}O_2$ gained by testosterone treatment (2.7 mL/kg per min) is greater than the increase of 0.7 to 1.1 mL/kg per min observed in early cardiac resynchronization therapy 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 to 52 weeks of testosterone therapy.^{19–22} Further, there is an improvement in New York Heart Association functional class, as 35% of the testosterone group had an improvement of at least 1 class compared with \approx 10% in the placebo group. This absolute difference in improvement is similar to that gained by cardiac resynchronization therapy compared with placebo (58% versus 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 because none of the trials in this meta-analysis showed improvement in left ventricular ejection fraction. 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 patients with HF. Other potential contributors to the functional improvement associated with testosterone therapy may include antiinflammatory and immunosuppressive effects; a rise in hemoglobin level¹⁵; 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 were all significantly improved after testosterone supplementation in this meta-analysis. Insulin resistance is common in patients with HF, occurring in up to 40% of patients.³¹ This metabolic disturbance may be related to low testosterone and can result in decreased glucose use by skeletal muscle, leading to muscle fatigue and wasting.^{32,33} Malkin et al³⁴ showed in a crossover study that insulin resistance as measured by HOMA-IR improves, whereas lean body mass increases after testosterone therapy in men.

Testosterone supplementation has also proven to be beneficial in other chronic disease states, such as cancer, chronic renal disease, pulmonary disease, and HIV, with benefits noted in improved voluntary muscle strength, lean muscle mass, and reduced fat mass.^{35–38} None of these publications (44 studies, 1459 patients), however, showed a reduction (or increase) in clinical end points, such as mortality or readmission.

Supratherapeutic doses of anabolic steroids, which differ in chemical structure and properties from testosterone, are associated with reduced cardiac function and adverse outcomes.³⁹ Despite the potential benefit of testosterone therapy, it also causes water and salt retention, and concern has arisen recently based on the TOM (Testosterone in Older Men with Mobility Limitations) trial, which was halted early because of a significantly higher risk of cardiovascular events in the testosterone-treated group.⁴⁰ However, patients with symptomatic HF 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 whether this contributed to the small excess of cardiovascular events. In addition, prior meta-analyses of 6 randomized controlled trials 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 with placebo, although there were only 21 events in 308 patients.^{15,41}

The present meta-analysis showed that there were no safety concerns reported in any of the trials, although data were limited given the small sample sizes and short durations of follow-up. Despite the concern with regard to the long-term risk of prostate cancer, currently available data do not support a link between testosterone replacement therapy and prostate cancer.^{42–47} Although there were no significant changes in level of prostate-specific antigen in any individual trial, the pooled estimates indicate a small, albeit significant increase in prostate-specific antigen levels. 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.

The present study had several 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 2 trials following patients for >12 weeks showed that the beneficial effects of testosterone occur early and are sustained for up to 12 months.^{19,21} Additionally, the 4 studies included used 2 different routes of administration for testosterone (intramuscular 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 men, 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 1 study that included 32 female patients with HF.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 patients with HF. Adequately powered RCTs are now required to assess the benefits of testosterone in this

high-risk population with regard to quality of life, clinical events, and safety.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Despite advances in evidence-based pharmacological therapies, patients with heart failure (HF) continue to exhibit significant morbidity and excess mortality at rates of up to 30% at 1 year. This high event rate, coupled with ongoing symptoms of fatigue, cardiac cachexia, and a metabolic shift toward catabolism, has led to an intense search for therapies to further improve HF symptoms. Low testosterone has been shown to be an independent predictor of reduced exercise capacity and poor clinical outcomes in patients with HF. Modestly sized randomized, placebo-controlled trials have explored the effects of testosterone therapy on exercise capacity in patients with HF, using a variety of exercise-based endpoints. In this meta-analysis of 4 published clinical trials involving 198 patients, testosterone therapy was associated with a significant improvement in exercise capacity compared with placebo. This improvement occurred without any improvement in myocardial structure or function. The mechanism for improvement in exercise capacity is complex and likely due to peripheral mechanisms. We also demonstrate the consistency of the effect of testosterone on the intermediate outcome of peak oxygen consumption, with a similar magnitude of effect to that of early development stages of angiotensin-converting enzyme inhibitors and cardiac resynchronization therapy. Although testosterone treatment has been linked to an increase in the number of cardiovascular events in asymptomatic patients without HF, there was no increase in clinical events across all 4 trials. Given the unmet clinical needs, the apparently favorable effects noted herein, and the limited number of patients reported to date in the literature, adequately powered randomized trials are needed to assess the benefits of testosterone on quality of life, clinical events, and safety in this high-risk population.