Low-Dose Testosterone Boosts Heart Function in Men

BY BRUCE JANCIN
Denver Bureau

BARCELONA — Modest-dose testosterone therapy brought significant functional and symptomatic improvement in men with moderate chronic heart failure in a yearlong double-blind randomized trial, Dr. Christopher J. Malkin said at the joint congress of the European Society of Cardiology and the World Heart Federation.

"This is the largest-ever prospective study of testosterone in chronic heart failure patients," said Dr. Malkin. "Testosterone is a naturally occurring and cheap hormone that seems to improve functional capacity and New York Heart Association class compared with placebo in men with chronic heart failure. We've seen effects with achievement of levels within the normal physiologic range."

The clinical improvements were all the more impressive given that many patients weren't able to take the full prescribed dose of testosterone replacement therapy because of recurrent skin rashes caused by the adhesive used in the 5-mg Androderm patches. Only 42 of the original 78 participants completed the full study year for that reason.

"The testosterone increases we achieved were actually very small. We'd hoped to get them up by 10 nmol/L; we achieved only about half of that," said Dr. Malkin of Royal Hallamshire Hospital, Sheffield, England.

The rationale behind the clinical trial was that heart failure (HF) entails a metabolic derangement characterized by catabolism and loss of skeletal muscle bulk from the prolonged activation of neurohormones and inflammatory cytokines. Androgens not only play a key role in maintaining physical strength in men, they also have vasodilatory and anti-inflammatory effects that are highly relevant in the HF setting.

Androgen levels decline with age and tend to run especially low in men with HF. In fact, at baseline, one-quarter of subjects were biochemically androgen deficient, as defined by a serum testosterone below 11 nmol/L.

The men at baseline had NYHA class II or III disease with left ventricular ejection fractions of 30%-35% and moderately elevated brain natriuretic peptide levels. Few of the men were cachectic; the average body mass index was 28 kg/m^2.

The primary study end point was change in exercise capacity as measured by an incremental shuttle walk test. The walk distance improved in the testosterone group by a mean of 19% over the 180 m at baseline, but it declined in the placebo group.

'This is the largest-ever prospective study of testosterone in chronic heart failure patients.'

DR. MALKIN

At follow-up, the testosterone group also displayed significantly increased handgrip strength. However, also in that group, there was a decrease in mean left ventricle (LV) mass index of 12.7 g/m^2 and LV cavity length increased by nearly 1 cm. "Whether the increase in LV cavity length and decrease in LV mass are clinically relevant needs to be investigated further. They could be emergent favorable left ventricular remodeling," Dr. Malkin said.

However, the testosterone-treated men showed no change over time in body mass index, brain natriuretic peptide levels, ejection fraction, several other echocardiographic parameters, thickness of skeletal muscle measured across the thigh, or any of the proinflammatory cytokines investigators measured.

Some remained androgen deficient despite testosterone therapy because the dose was so small. "If we can improve their testosterone levels further, we may see even better effects than those in this study," he said.

Some audience members raised concerns about possible cardiotoxic effects of exogenous testosterone in a vulnerable HF population.

"I don't think there's any doubt that supraphysiologic levels of testosterone cause cardiotoxicity. But we're not advocating supraphysiologic levels at all. Our target was high physiologic levels—20-30 nmol/L, levels about what we'd see in elite athletes," Dr. Malkin replied.

The investigators are planning a new study of testosterone therapy with or without a structured aerobic exercise program. They plan to scrap the poorly tolerated patch in favor of either a gel preparation or 3-month depot injections, which patients most prefer. ■

Interim Data Suggest Sildenafil May Benefit Some HF Patients

BY SHERRY BOSCHERT
San Francisco Bureau

SEATTLE — A 12-week study of sildenafil therapy in patients with heart failure due to left ventricular dysfunction and secondary pulmonary hypertension is continuing after an interim analysis found neither therapeutic futility nor overwhelming improvements in exercise capacity, Dr. Gregory Lewis said.

Speaking at the annual meeting of the Heart Failure Society of America, he did not give more specific results on exercise capacity changes in the 28 patients studied so far, but reported improvements in two secondary end points of the trial. In addition, there's no sign so far of any increase in adverse events related to the sildenafil therapy, said Dr. Lewis of Massachusetts General Hospital, Boston, and his associates.

He has no association with the company that makes sildenafil.

The double-blind study randomizes patients with New York Heart Association class III or IV systolic heart failure and secondary pulmonary hypertension to 12 weeks of placebo or oral sildenafil titrated up to 75 mg t.i.d. Twelve of 14 patients per group in the interim analysis completed the protocol.

At week 12, patients in the sildenafil group walked a mean 13% farther on the 6-minute walk test, a significant improvement compared with baseline and compared with the placebo group.

This result is consistent with a mean placebo-corrected 13% increase in the 6-minute walk distance demonstrated in the Sildenafil Citrate Therapy for Pulmonary Arterial Hypertension study, which gave similar doses of sildenafil to patients with idiopathic and other forms of pulmonary arterial hypertension unrelated to left ventricular systolic dysfunction (N. Engl. J. Med. 2005;353:2148-57).

In the current study, five patients in the sildenafil group improved their scores on the Minnesota Living with Heart Failure questionnaire, creating a significant difference in quality-of-life scores between the sildenafil and placebo groups at week 12.

The rates of adverse events did not differ significantly between the groups except in the number of hospitalizations for heart failure, for which there was one in the sildenafil group, and seven in five patients on placebo. The safety of chronic sildenafil therapy has not been studied extensively in this population before.

Dr. Lewis cautioned that the interim analysis rests on small numbers, and that results need to be validated in larger cohorts.

In an earlier study, Dr. Lewis and his associates found that acute administration of a single 50-mg oral dose of sildenafil lowered pulmonary arterial pressures, improved cardiac output, and increased exercise tolerance in patients with systolic heart failure and secondary pulmonary hypertension. ■

Resistance to Aspirin Tx Seen In 20% of Heart Failure Patients

BY SHERRY BOSCHERT
San Francisco Bureau

SEATTLE — Blood tests on 507 patients seen in emergency departments for chest pain found resistance to aspirin in 20% of those with a history of heart failure and in 12% of those without heart failure, Dr. Lori B. Daniels reported in a poster presentation at the annual meeting of the Heart Failure Society of America.

"Physicians should be aware of the high rate of aspirin nonresponsiveness in patients with heart failure, because they may be susceptible to thrombotic events" even if treated with aspirin, and they may need other antithrombotic therapy, said Dr. Daniels of the University of California, San Diego, and her associates.

Aspirin prevents MI, stroke, or other vascular events by causing platelet dysfunction so that platelets do not aggregate. It irreversibly inhibits platelet cyclooxygenase, a key enzyme in prostaglandin synthesis, so platelets lose the capacity to synthesize thromboxane A2, an inducer of platelet aggregation with vasoconstrictive properties.

Between 8% and 18% of patients treated with aspirin, however, develop recurrent vascular events within 2 years, a phenomenon described as aspirin resistance "or perhaps, more accurately, as aspirin nonresponsiveness," the investigators wrote.

They took blood samples from patients with suspected acute coronary syndromes seen at five medical centers. All were on outpatient aspirin therapy or were given an aspirin when they arrived at the emergency department. The 25% of patients with a history of heart failure were older than those without heart failure (62 vs. 58 years) and were more likely to be taking aspirin as an outpatient (81% vs. 60%), but the two groups did not differ by sex or body mass index.

Blood samples were tested using the Ultegra Rapid Platelet Function Assay on a VerifyNow testing device. The Ultegra assay is a turbidimetric-based optical detection system that measures platelet-induced aggregation as an increase in light transmittance. Aspirin nonresponsiveness was defined as an "aspirin reaction unit" value of at least 550. Results showed a mean of 479 aspirin reaction units in patients with a history of heart failure, compared with 458 units in patients without heart failure. None of the investigators are associated with Accumetrix, which makes the VerifyNow device.

Patients with heart failure who do not respond to aspirin may be susceptible to thrombotic events.

DR. DANIELS

Heart failure patients were more likely to have a history of hypertension (88% vs. 71%), coronary artery disease (65% vs. 32%), MI (55% vs. 23%), diabetes (49% vs. 28%), chronic renal insufficiency (28% vs. 6%), and tobacco use (63% vs. 51%), compared with non–heart failure patients. Those with heart failure averaged 4 years of aspirin use, compared with 2 years in patients without. ■