Recent Landmark Drug Trials in Heart Failure Management

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Introduction

More than a decade and several thousands of procedures Heart failure (both acute as well as chronic) is a common and serious health problem. Even with existing treatment, which has substantially improved outcomes, prognosis is fairly poor. Standard pharmacological treatment includes diuretics, β-blockers and renin–angiotensin aldosterone system (RAAS) antagonists. Development of newer therapeutic approaches for the treatment of this disorder is essential. We discuss here few recent drug trials with the potential to change management of heart failure favorably.

EMPHASIS-HF Trial. Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms

Zannad F, McMurray JJ, Krum H, et al. *N Engl J Med.* 2011;364:11–21.

In this randomized, double-blind trial, 2737 patients with New York Heart Association class II heart failure and an ejection fraction <35% were assigned to receive eplerenone (up to 50 mg daily) or placebo, in addition to recommended therapy. The primary outcome was a composite of death from cardiovascular causes or hospitalization for heart failure. After a median followup period of 21 months, the primary outcome occurred in 18.3% of patients in the eplerenone group as compared with 25.9% in the placebo group (hazard ratio, 0.63; 95% confidence interval [CI], 0.54–0.74; $p<0.001$). A total of 12.5% of patients receiving eplerenone and 15.5% of those receiving placebo died (hazard ratio, 0.76; 95% CI, 0.62–0.93; $p=0.008$). Deaths due to cardiovascular causes occurred in 10.8% in eplerenone group and 13.5% in placebo group (hazard ratio, 0.76; 95% CI, 0.61–0.94; $p=0.01$). Hospitalizations for heart failure and for any cause were also reduced with eplerenone. A serum potassium level exceeding 5.5 mmol per liter occurred in 11.8% of patients in the eplerenone group and 7.2% of those in the placebo group ($p<0.001$).

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Perspective

We know that mineralocorticoid antagonists improve survival among patients with chronic, severe systolic heart failure and heart failure after myocardial infarction. In this trial it has been seen that eplerenone, as compared with placebo, reduced both the risk of death and the risk of hospitalization among patients with systolic heart failure and mild symptoms.

SHIFT Trial (Systolic Heart Failure Treatment with the If inhibitor Ivabradine Trial)

Swedberg K, Komajda M, Bohm M, et al., on behalf of the SHIFT Investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet.* 2010;376:875–85.

Raised resting heart rate is a risk factor for adverse outcomes in chronic heart failure. This study assessed the effect of heart-rate reduction by the selective sinus-node inhibitor ivabradine on outcomes in heart failure. It was randomized, double-blind, placebo-controlled, parallel-group study. The study was conducted in 677 centers in 37 countries. Patients were eligible if they had symptomatic heart failure and a left-ventricular ejection fraction of ≤35%, were in sinus rhythm with heart rate ≥70 beats per min, had been admitted to hospital for heart failure within the previous year, and were on stable background treatment including a β-blocker if tolerated. Main exclusion criteria were recent (<2 months) myocardial infarction, ventricular or atrioventricular pacing operative for 40% or more of the day, atrial fibrillation or atrial flutter, and symptomatic hypotension. Patients were randomized to ivabradine titrated to a maximum of 7.5 mg twice daily or matching placebo. The primary endpoint was the composite of cardiovascular death or hospital admission

for worsening heart failure. Here 6558 patients were randomly assigned to treatment groups. After a median followup of 22.9 months, 793 (24%) patients in the ivabradine group and 937 (29%) of those taking placebo had a primary endpoint event (HR 0.82, 95% CI 0.75–0.90, $p<0.0001$). There were fewer hospital admissions for worsening heart failure (514 [16%] ivabradine vs. 672[21%] placebo; HR 0.74, 0.66–0.83; $p<0.0001$) and deaths due to heart failure (113 [3%] vs. 151 [5%]; HR 0.74, 0.58–0.94, $p=0.014$). Fewer serious adverse events occurred in the ivabradine group (3388 events) than in the placebo group (3847; $p=0.025$).

Perspective

This trial confirms that heart rate plays an important part in the pathophysiology of heart failure and supports the concept that reduction in heart rate contributes significantly to beneficial outcomes in patients with heart failure. In patients of systolic heart failure, in sinus rhythm, and receiving the usual care and who have heart rates . 70/min but are intolerant to higher doses of ƒÀ-blocker, ivabradine can improve clinical outcomes.

RELAX-AHF Trial (The RELAXin in Acute Heart Failure Trial)

Teerlink JR, Cotter G, Davidson BA, et al., for the RELAXin in Acute Heart Failure (RELAX-AHF) Investigators. Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial. *Lancet.* 2013;381:29–39.

Serelaxin is recombinant human relaxin-2 which is a naturally occurring peptide that regulates maternal adaptations to pregnancy. It increases arterial compliance, cardiac output, and renal blood flow and these effects may be potentially relevant to the treatment of acute heart failure. The RELAX-AHF trial tested the hypothesis that serelaxin-treated patients would have greater dyspnoea relief compared with patients treated with standard care and placebo. RELAX-AHF was a prospective, randomized, double blind, placebo-controlled, parallel-group trial comparing serelaxin with placebo in patients admitted to hospital for acute heart failure. It enrolled patients at 96 sites in 11 countries. Patients were eligible for enrolment if they presented within the previous 16 hours with dyspnoea at rest or with minimum exertion, pulmonary congestion on chest radiograph, and BNP 350 ng/L or higher or NT-proBNP 1400 ng/L or higher, as well as mild to moderate renal dysfunction, SBP greater than 125 mmHg, and treatment with at least 40 mg intravenous furosemide or its equivalent before screening. The exclusion criteria included treatment with other intravenous heart failure drugs (except intravenous nitrate ≤ 0.1 mg/kg per hour in patients with SBP at screening of >150 mmHg) or mechanical support within 2 hours before screening, signs of active infection, known significant pulmonary or valvular disease, acute heart failure due to significant arrhythmias, acute coronary syndrome diagnosed within 45 days, or a troponin concentration three times or more higher than the level diagnostic of myocardial infarction. It randomized 1161 patients to one of the two treatment groups (serelaxin 30 µg/kg per day or placebo). The primary endpoints evaluating dyspnoea improvement were change from baseline in the visual analogue scale area under the curve (VAS AUC) to day 5 and the proportion of patients with moderate or marked dyspnoea improvement measured by Likert scale during the first 24 hours, both analyzed by intention to treat. Serelaxin improved the VAS AUC primary dyspnoea endpoint by 19% (448 mm × h, 95% CI 120–775; p=0.007) compared with placebo, but had no significant effect on the other primary endpoint (Likert scale; p=0.70). No significant effects were recorded for the secondary endpoints of cardiovascular death or readmission to hospital for heart failure or renal failure. Serelaxin treatment was associated with significant reductions in other prespecified additional endpoints, including fewer deaths at day 180 (placebo, 65 deaths; serelaxin, 42; HR 0.63, 95% CI 0.42–0.93; p=0.019).

Perspective

In RELAX-AHF, a 48-hour infusion of serelaxin resulted in mild improvements in measures of dyspnoea, associated with significant reductions in early worsening heart failure events, signs and symptoms of congestion, initial length of hospital stay, and duration of intensive care. However, there was no improvement in readmission to hospital for heart failure or renal failure. A 37% reduction in cardiovascular and all-cause mortality was also noted in the serelaxin-treated patients.