SHIFT Study
– BACKGROUNDER –

About SHIFT

SHIFT (**S**ystolic **H**eart Failure Treatment with the I_f Inhibitor Ivabradine **T**rial) is a randomised, double-blind study designed to compare ivabradine (Procoralan®) with placebo on outcomes in patients with moderate to severe chronic heart failure (CHF), left-ventricular ejection fraction and those who had been hospitalised for worsening heart failure within the previous 12 months. The study was designed to assess whether Procoralan can improve cardiovascular outcomes and symptoms and quality of life when added to standard therapy in patients with CHF and systolic dysfunction.

Rationale

CHF is a common syndrome with a prevalence estimated at approximately 2-3% worldwide.[1] Despite recent improvements in standard of care, heart failure remains to be a disabling disorder affecting quality of life with a poor prognosis for patients. Elevated resting heart rate is a highly significant risk predictor of mortality and hospitalisation in CHF patients.[2] Standard therapy with beta-blockers has improved morbidity and mortality in patients with CHF[3], however in clinical practice, only a relatively small proportion of patients with heart failure receive the recommended target doses of beta-blockers.[4-7] Moreover, despite the benefits of beta blockers the mortality and morbidity in heart failure remains high thus necessitating the need for new therapy. Procoralan specifically reduces heart rate without the unwanted effects associated with beta-blockers. It works by inhibiting the I_f current that regulates the pacemaker activity of the sinoatrial node cells.[8]

Studies on normal, healthy hearts show that Procoralan does not affect other myocardial ion channels or receptors and it has no unwanted beta-blocker type effects.[9]

In patients with advanced heart failure and poor left-ventricular function, acute administration of intravenous Procoralan effectively decreased heart rate, but preserved cardiac output and was well tolerated.[10]

Specific heart rate lowering with Procoralan could particularly benefit several subgroups of patients with systolic heart failure, including:

(i) those in whom beta-blockers are contraindicated or not tolerated

(ii) those whose beta-blocker dose is limited due to adverse effects such as hypotension, fatigue

(iii) those whose heart rate remains high (≥70 b.p.m.) in spite of the maximum tolerated dose of beta-blockers

Aim

SHIFT aims to address a novel therapeutic approach to the treatment of CHF and whether Procoralan, a new agent that reduces heart rate by direct sinus node inhibition, can improve cardiovascular outcomes, symptoms and quality of life when added to standard therapy in patients with CHF and systolic dysfunction.

Design

SHIFT is an event-driven, international, multicentre, randomised, double-blind, placebo-controlled, parallel group study in patients with moderate to severe CHF and systolic left ventricular dysfunction. The study included approximately 6,500 patients at 700 centres in 37 countries worldwide. After a run-in period of 14 days without study treatment, eligible patients were randomised to receive Procoralan or placebo in addition to treatments appropriate to their chronic heart failure. These included ACE-I and/or an angiotensin II receptor blocker, a beta-blocker, a diuretic, an aldosterone antagonist. The starting dose of either Procoralan or placebo was 5mg daily. After a 14 day titration period, at Day 14, the dose was increased to 7.5mg twice daily. If resting heart rate fell below 50 b.p.m or patients experienced bradycardia-like symptoms, the dose was reduced to 2.5mg twice daily. If heart rate was between 50 and 60 b.p.m. dose was maintained at 5mg twice daily. The double-blind treatment period lasted approximately 12–48 months. The first patient was randomised in October 2006 and the study ended in May 2010.

Participating patients

Patients were male or female with effective contraception, aged ≥18years with stable symptomatic chronic heart failure for ≥4 weeks and a prior hospitalisation for worsening heart failure within the previous 12 months. Left-ventricular systolic dysfunction defined by

an ejection fraction ≤35% was required. Patients were also in sinus rhythm with a resting heart rate ≥70 b.p.m. as measured on 12-lead ECG performed after at least 5 minute rest on the two consecutive visits before randomisation. Main exclusion criteria include recent myocardial infarction, ventricular, or atrioventricular pacing that is operative for more than 40% of the day, atrial fibrillation or symptomatic hypotension.

Data collection

Baseline assessments performed at the selection included verification of inclusion and exclusion criteria, a relevant medical history, physical examination including systolic and diastolic blood pressure, recording of concomitant treatments, assessment of NYHA heart failure class, measurement of left-ventricular ejection fraction (if no evaluation available in previous 3 months), heart rate (by 12-lead ECG) and blood tests, including total and LDL cholesterol. During follow-up, the occurrence of pre-specified events (defined as deaths and hospitalisations from any cause), evaluation of NYHA heart failure class, a physical examination, heart rate (by 12-lead ECG) blood pressure, and the occurrence of adverse events was recorded at each study visit. In addition, at 4 months and at the annual visits (months 12 and 24), global assessments of heart failure symptoms were performed using investigator and patient questionnaires, and fasting blood samples were obtained for clinical laboratory tests.

Study endpoints

The primary endpoint was cardiovascular death or hospitalisation for worsening heart failure. The first secondary endpoint was cardiovascular death or hospitalisation for worsening heart failure in patients receiving at least 50% of the target daily dose of beta-blockers at randomisation. Other secondary endpoints included all-cause death, any cardiovascular death, hospitalisation for worsening heart failure, all-cause hospitalisation, any cardiovascular hospitalisation and death from heart failure, hospitalisation for non-fatal myocardial infarction.

Results

Results from SHIFT will be presented at the ESC congress 2010 in Stockholm, Sweden, on Sunday 29th August (date TBC).

References

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