Systolic Heart failure treatment with the IF inhibitor ivabradine Trial - SHIFT

American College of Cardiology, Aug 29, 2010

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Trial Sponsor: Servier
Date Presented: 01/01/2010
Date Published: 01/01/2010
Date Updated: 08/29/2010
Original Posted Date: 08/29/2010

Description:

The goal of the trial was to evaluate the heart rate reducing agent ivabradine compared with placebo among patients with chronic heart failure. Ivabradine inhibits the If current in the sinoatrial node.
Hypothesis:

Ivabradine will be more effective at improving cardiovascular outcomes.

Study Design
- Randomized
- Parallel
- Placebo Controlled

Patient Populations:
- Patients at least 18 years of age with moderate to severe heart failure on optimal medical therapy
- Left ventricular ejection fraction ≤35%
- Resting heart rate ≥70 bpm
- Sinus rhythm
- Hospital admission for heart failure in the last 12 months

Number of screened applicants: 7,411
Number of enrollees: 6,558
Duration of follow-up: median 22.9 months
Age range: mean 61 years
Percentage female: 24%
Ejection fraction: 29%
NYHA class II: 49%, and NYHA class III/IV: 51%

Primary Endpoints:
- Cardiovascular mortality or hospitalization for heart failure

Secondary Endpoints:

- All-cause mortality, cardiovascular mortality, or heart failure mortality
- All-cause hospitalization, cardiovascular hospitalization, or heart failure hospitalization
- Cardiovascular mortality, heart failure hospitalization, or nonfatal myocardial infarction
- NYHA class
- Global patient assessment

Drug/Procedures Used:

Eligible patients with moderate to severe chronic heart failure and resting heart rate ≥70 bpm were randomized to ivabradine 5 mg twice daily (n = 3,268) versus placebo twice daily (n = 3,290). Ivabradine was titrated up or down according to tolerability and heart rate.
Concomitant Medications:

At baseline, in the ivabradine group, the use of beta-blockers was 89% (although only 26% at target dose), angiotensin-converting enzyme inhibitors and/or angiotensin-receptor blockers was 91%, and aldosterone antagonists was 61%.

Principal Findings:

Overall, 6,558 patients were randomized. In the ivabradine group, the mean age was 61 years, 24% were women, 30% were diabetics, 68% had an ischemic etiology, New York Heart Association (NYHA) class II was 49%, NYHA class III/IV was 51%, mean heart rate was 80 bpm, mean left ventricular ejection fraction was 29%, mean blood pressure was 122/76 mm Hg, and mean estimated glomerular filtration rate was 75 ml/min/1.73 m2.

At 32 months, mean heart rate was 67 bpm in the ivabradine group versus 75 bpm in the placebo group ($p < 0.050$).

Cardiovascular mortality or heart failure hospitalization was 14.5% in the ivabradine group versus 17.7% in the placebo group ($p < 0.0001$). This benefit was especially pronounced in those with a baseline resting heart rate ≥77 bpm. Cardiovascular mortality was 7.5% versus 8.3% ($p = 0.13$), and heart failure hospitalization was 9.4% versus 12.7% ($p < 0.0001$), respectively.

Symptomatic bradycardia was 5% versus 1% ($p < 0.0001$) and asymptomatic bradycardia was 6% versus 1% ($p < 0.0001$), although total adverse events were 75% versus 74% ($p = 0.30$), respectively.

Interpretation:

Among patients with moderate to severe heart failure, the use of the heart rate reducing agent ivabradine was beneficial. This agent reduced the composite outcome of cardiovascular mortality or heart failure hospitalization compared with placebo. While well tolerated, ivabradine was associated with more symptomatic and asymptomatic bradycardia. This represents a new approach to heart failure management, especially in patients who are unable to tolerate high-dose beta-blockers. Since ivabradine acts at the sinus node, it is not indicated in patients with atrial fibrillation.

References:

Swedberg K, Komajda M, Böhm 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.

Substudy: Böhm M, Swedberg K, Komajda M, et al., on behalf of the SHIFT Investigators. Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial. Lancet 2010;376:886-94.

Presented by Dr. Michel Komajda at the European Society of Cardiology Congress, Stockholm, Sweden, August 2010.

Clinical Topics: Arrhythmias and Clinical EP, Heart Failure and Cardiomyopathies, Implantable Devices, EP Basic Science, Acute Heart Failure

Keywords: Follow-Up Studies, Blood Pressure, Sinoatrial Node, Heart Rate, Benzazepines, Heart Failure, Glomerular Filtration Rate, Stroke Volume, Bradycardia, Diabetes Mellitus

- See more at: https://www.acc.org/latest-in-cardiology/clinical-trials/2012/05/20/16/30/shift#sthash.hjObnKuM.dpuf