BEAUTIFUL Trial Fails to Meet Primary Endpoint

Highlights from the
European Society of Cardiology 2008 Annual Meeting

Although the BEAUTIFUL (morBidity-mortality EvAlUaTion of the I_f inhibitor ivabradine in patients with coronary artery disease and left ventricULar dysfunction) trial (NCT00143507) failed to meet its primary composite endpoint of cardiovascular death, admission to hospital for acute myocardial infarction (MI), and hospitalization for new-onset or worsening heart failure (HF), it significantly reduced important secondary endpoints, such as hospitalization for fatal or non-fatal MI and coronary revascularization. In addition, BEAUTIFUL has provided valuable new mechanistic information in HF, indicating a threshold for the deleterious effect of heart rate (HR) in patients with stable coronary artery disease (CAD) and left ventricular dysfunction (LVD).

Prior studies have demonstrated that elevated resting HR is associated with an increased risk of all-cause mortality, cardiovascular mortality, and development of cardiovascular disease in the general population, as well as in individuals with preexisting CAD [Graham I et al. *Eur Heart J* 2007; Fox K et al. *J Am Coll Cardiol* 2007; Palatini P and Julius S. *Clin Exp Hypertens* 2004].

Ivabradine, a selective HR-lowering agent, acts on the sinoatrial node, providing rate reduction without altering other cardiac functions. In a rat model of cardiac failure, it increased stroke volume and improved left ventricular function [Mulder P et al. *Circulation* 2004]. A preliminary study in patients with CAD and moderate LVD also has suggested that ivabradine has beneficial effects on left ventricle geometry [Jondeau G et al. *Eur Heart J 2004*].

The BEAUTIFUL trial was designed to assess whether the addition of ivabradine to standard treatment would reduce cardiovascular death and morbidity in patients with HF and to evaluate the role of HR as a predictor of risk in patients with CAD and LVD [Fox K et al. *Lancet* 2008].

BEAUTIFUL was a randomized, double-blind, placebo-controlled trial that was conducted at 781 centers worldwide. Eligible patients included men and women aged 55 years or older (≥18 years if diabetic) with documented CAD and a left ventricular ejection fraction (LVEF) <40%. Patients had to be in sinus rhythm with a resting HR ≥60 beats per minute (bpm). The trial also required that subjects were clinically stable for 3 months with regard to angina and HF symptoms and receiving conventional cardiovascular medication at constant doses for 1 month.

The primary study endpoint was a composite of cardiovascular mortality, hospital admission for acute MI, and hospitalization for new-onset or worsening HF. Secondary endpoints included all-cause mortality, cardiac death, cardiovascular death, hospital admission for new/worsening HF, the composite of hospital admission for fatal and non-fatal acute MI or unstable angina, and coronary revascularization.

The study population included 10,917 subjects (mean age 65 years; 83% men). Subjects initially were assigned to receive ivabradine 5 mg (n=5479) or matching placebo (n=5438) twice daily. Follow-up visits were conducted at Week 2, at Months 1, 3, and 6, and every 6 months thereafter. At Week 2, the dose for subjects whose resting HR was ≥60 bpm was increased to 7.5 mg twice daily (or matching placebo).

Patients continued to receive their usual cardiovascular medical treatment throughout the study. Concomitant treatments included β-blockers (87%), angiotensin-converting enzyme inhibitors (90%), aspirin or antithrombotic agents (94%), statins (74%), antialdosterone

agents (27%), and diuretics (59%). At baseline, the overall population had a mean resting HR of 71.6 bpm. Mean LVEF was 32.4%. Approximately 90% of all patients had a history of MI; 70% had hypertension and 40% were diabetics. Median duration of follow-up was 19 months.

Subjects who received ivabradine had a mean reduction in HR of 6 bpm at 12 months and 5 bpm at 24 months. This reduction did not translate to an improvement of the primary endpoint in the overall population (HR 1.00; 95% CI, 0.91 to 1.1; p=0.94). HR reductions in the subgroup of subjects whose HR was ≥70 bpm were 9 bpm at 6 months, 7.9 bpm at 12 months, and 6.9 bpm at 24 months. In this group, there was a significant reduction in the secondary outcomes of hospital admission for fatal and non-fatal MI (0.64; 95% CI, 0.49 to 0.84; p=0.001) and coronary revascularization (0.70; 95% CI, 0.52 to 0.93; p=0.016).

The frequency of serious adverse events was not different between treatment groups (22.5% vs 22.8%; p=0.70); however, more patients in the ivabradine group discontinued treatment (28%) versus those who received placebo (16%). The most common reason for treatment discontinuation in the ivabradine group was bradycardia.

In commenting on the BEAUTIFUL study, Sidney C. Smith, MD, University of North Carolina, Chapel Hill, NC, noted that while the results of BEAUTIFUL do not change the guidelines for treatment of LVD, it does point to the need for prospective studies of ivabradine in subjects with CAD and HR ≥70 bpm.

The results of this study were presented by Kim Fox, MD, Imperial College, London, UK, Chairman of the BEAUTIFUL Executive Committee, and published simultaneously online in *The Lancet* [Fox K et al. *Lancet* 2008].

Intensified Medical Therapy Does Not Appear to Benefit Elderly Heart Failure Patients

Intensified NT-BNP (N-terminal B-type natriuretic peptide)-guided therapy is not more effective than standard, symptom-guided therapy in reducing death and all-cause hospitalization among elderly congestive heart failure (CHF) patients, researchers reported at the European Society of Cardiology (ESC) Congress 2008 in Munich. However, response to treatment differed between age groups, wherein patients aged 60 to 74 years achieved significantly reduced mortality and improved survival free of hospitalization for heart failure (HF) in contrast to with subjects aged 75 years and older, where there was no difference between the two treatment strategies.

"Intensified BNP-guided therapy may be considered in younger patients to reduce disease-specific risk and mortality," said presenter and trial leader Hans-Peter Brunner-La Rocca, MD, University Hospital, Basel, Switzerland. "However, patients over 75 show no benefit," he added.

Dr. Brunner-La Rocca noted that previous studies had suggested a possible outcome benefit for HF patients who were treated with BNP-guided therapy. The purpose of this study was to test this hypothesis specifically in an elderly population.

Such research is particularly important in elderly patients, who are physically less active and in whom symptoms are more obscure. Dr. Brunner-La Rocca also emphasized that even though elderly patients represent the majority of HF patients, they have been underrepresented in randomized trials thus far.

Investigators for TIME-CHF (Trial of Intensified [BNP-guided] versus standard [symptom-guided] Medical therapy in Elderly patients with Congestive Heart Failure; ISRCTN43596477) enrolled 499 Swiss and German subjects from 15 participating hospitals in the 18-month study. Enrollment criteria included patients aged 60 or older (with no upper limit), symptomatic HF, New York Heart Association (NYHA) ≥ class II despite therapy, left ventricular ejection fraction (LVEF) ≤45%, HF hospitalization within the last year, and elevated NT-BNP (>400 pg/ml for those aged 60 to 74 years and >800 pg/ml for those aged 75 years and older).

Exclusion criteria included dyspnea that was not mainly caused by CHF, significant uncorrected valvular heart disease, acute coronary syndrome within 10 days, angina pectoris due to ischemia, PCI (percutaneous coronary intervention) within 1 month or CABG (coronary artery bypass graft surgery) within 3 months, body mass index >35, serum creatinine >2.5 mg/dl and life expectancy of less than 3 years (unrelated to cardiovascular disease).

Participants were randomized to standard versus intensified therapy and stratified by age (75 years and older vs 60 to 74 years). Primary study endpoints were survival free of any hospitalization and quality of life with secondary endpoints of survival and survival free of HF hospitalization.

The aim of therapy in the standard treatment group (n=248) was NYHA ≤II, blinded to NT-BNP results. The aim in the intensified treatment group (n=251) was NT-BNP <400 pg/ml (60-74 years) or <800 pg/ml (75 years and older) and NYHA ≤II.