



BEAUTIFUL

Morbidity-mortality Evaluation of the I_f
inhibitor ivabradine in patients with coronary
disease and left ventricular dysfunction

MEDICAL PRESS RELEASE

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From the I_f pacemaker current discovery to the BEAUTIFUL study with ivabradine: landmark research and development in cardiovascular disease

The discovery of the I_f pacemaker current in 1979 by Professor D. DiFrancesco led to the development of ivabradine (Procoralan), the first selective and specific I_f current inhibitor of the sinus node. Ivabradine is the only pure heart rate-reducing treatment and has been available for clinical use in stable angina since January 2006. Moreover, there is also growing evidence that elevated heart rate is associated with an increased risk of cardiovascular events and vice versa. The landmark BEAUTIFUL study was therefore initiated to assess for the first time the role of heart rate and to what extent pure heart rate reduction with ivabradine reduces cardiac events in patients with stable coronary artery disease. The results of the BEAUTIFUL study should be released at the European Society of Cardiology Congress in August 2008.*

- The discovery of the I_f pacemaker current

Heart rate (pulse) is a sign of life. In the last decade, evidence has been growing through large-scale epidemiological studies that elevated heart rate is associated with an increased risk of cardiovascular events and vice versa. This association has been reported in apparently healthy individuals and in patients across the cardiovascular disease spectrum^{1,2}.

Research was undertaken to identify new and effective ways to reduce heart rate exclusively. The I_f pacemaker current was discovered in 1979 by Professor Dario DiFrancesco, director of the Laboratory of Molecular Physiology and Neurobiology at the University of Milan in Italy. The I_f current is a mixed $\text{Na}^+ - \text{K}^+$ inward current activated by hyperpolarization and modulated by the autonomic nervous system according to a mechanism regulating the heart rate. The relevance of the I_f current in the generation of heart rate and heart rate control made it an ideal target for drug development.

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- The first selective and specific I_f current inhibitor Procoralan®

Attempts to selectively and specifically inhibit the I_f current led to the discovery of Procoralan® (ivabradine). Procoralan is a breakthrough in cardiology as it is the first and only treatment to provide pure heart rate reduction while fully preserving myocardial contractility, atrioventricular conduction, and ventricular repolarization as well as blood pressure. Procoralan, first launched for clinical use in January 2006, is currently available in around 45 countries in Europe and other parts of the world. It is well established that Procoralan relieves ischemia and angina. However, the role of Procoralan in the management of coronary patients seems to be much larger.

- The BEAUTIFUL study

Coronary artery disease (CAD) is the leading cause of death and the World Health Organization predicts that it will remain so for at least the next 20 years³. As resting heart rate is directly correlated with increase in cardiovascular mortality, pure heart rate reduction with Procoralan could be an effective way to reduce cardiovascular events in CAD. The BEAUTIFUL (morBidity-mortality EvAIUaTion of the I_f inhibitor ivabradine in patients with CAD and left ventricULar dysfunction) trial was initiated in 2005 under the guidance of an independent Executive Committee. Almost 11 000 patients with documented stable CAD and associated left ventricular dysfunction from 33 countries have been enrolled in the BEAUTIFUL study. The baseline heart rate in these patients is 72 beats per minute, which is consistent with recent observational studies. Fifty percent of patients have a heart rate above 70 beats per minute. Most patients are already receiving guidelines-recommended optimal cardiovascular therapy: antiplatelet agents (94%), angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (91%), β -blockers (87%), as well as lipid-lowering agents (76%).

Commenting on the trial, Professor Gabriel Steg, Member of the Executive Committee of BEAUTIFUL, said: "It is a rare occurrence in medicine that a risk factor is being tested with one large clinical trial, which is BEAUTIFUL." He went on to say: "BEAUTIFUL will answer an important question—will pure heart rate reduction with ivabradine reduce cardiovascular events over and above the optimal current preventive therapy? The results of the BEAUTIFUL trial are eagerly awaited by the scientific community as these results could have a huge impact in the management of coronary patients."

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- The BEAUTIFUL study results will be available in a few weeks

The study is now completed and a recent publication in *Cardiology* provides the full details of the study population⁴. The BEAUTIFUL trial results should be announced during the hotline session of the European Society of Cardiology Congress in Munich, Germany.

For more information on the BEAUTIFUL study please visit:
www.beautiful-study.com

Note to editors:

BEAUTIFUL (morbidity-mortality Evaluation of the I_f inhibitor ivabradine in patients with coronary heart disease and left ventricular dysfunction) is a multicenter, multinational, randomized, double-blind, placebo-controlled, parallel-group trial. The primary end point is the composite of CV death, hospitalization for acute myocardial infarction, or new or worsening heart failure. On entering the trial, 87% of patients were receiving treatment with β -blockers, 89% with renin-angiotensin system agents, 94% with antithrombotic agents, and 76% with lipid-lowering agents. 37% of patients also had diabetes and 40% had metabolic syndrome.

The members of the Executive Committee of BEAUTIFUL are: Prof R. Ferrari, Italy; Prof I. Ford, UK; Prof K. Fox, UK; Prof P. Steg, France; Prof M. Tendera, Poland.

Ivabradine (Procoralan®)* is the first selective and specific inhibitor of the sinus node I_f current and is the first agent to reduce heart rate exclusively while fully preserving myocardial contractility, atrioventricular conduction, and ventricular repolarization as well as blood pressure. All these properties result in ivabradine having a powerful anti-ischemic efficacy and an optimal cardiac performance. Ivabradine is currently indicated for the treatment of stable angina in patients with sinus rhythm and with contraindications or intolerance to β -blockers.

**Depending on the country, ivabradine is available as Procoralan®, Coralan®, Coraxan®, or Corlantor®*

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About Servier

Servier is France's leading independent pharmaceutical company and the country's second largest drug company. Servier is present in 140 countries. R&D at Servier spans a range of therapeutic fields, with the main areas of focus being cardiovascular disease, neuroscience, oncology, metabolic disorders, and rheumatology. In the field of cardiovascular disease in particular, Servier is one of the principal research organizations dedicated to the development of new medicines. Servier has a long-standing interest in the field of cardiovascular disease, as attested by the fact that 63% of Servier's global turnover from medicines is made up of drugs targeting cardiovascular diseases.

References:

1. Diaz A, et al. *Eur Heart J*. 2005;26:967-974.
2. Resting Heart Rate in Cardiovascular Disease. *J Am Coll Cardiol*. 2007;50:823-830.
3. Projections of Global Mortality and Burden of Disease from 2002 to 2030 *PLoS Med* 3(11): e442. doi:10.1371/journal.pmed.0030442.
4. BEAUTIFUL Study Group. *Cardiology*. 2008;110:271-282.