The BEAUTIFUL trial: Drugs Supplement on Ivabradine

The Drugs Supplement (Adis), which promotes optimum pharmacotherapy by providing a programme of review articles covering the most important aspects of clinical pharmacology and therapeutics, has a review on $\mathbf{I(f)}$ Inhibition by Ivabradine in vol. 67, Supplement. 2 (pp. 1-49) of 2007.

The foreword and 5 chapters discuss the basis for exploring the full range of application of a heart rate reduction and pure heart rate reduction in particular as a powerful tool that promises substantial benefit in mitigating cardiovascular pathophysiology and disease.

It discusses:

1. Heart rate is a key determinant of ischemia and emerging evidence suggests that elevated heart rate is an independent predictor of morbidity and mortality across the cardiovascular disease continuum. Elevated heart rate is known to promote atherosclerosis and can lead to plaque rupture leading to cardiovascular events.

2. The cellular basis for the control of heart rate - the so called ‘funny’ (pacemaker, $I_f$) current, first described 30 years ago in sinoatrial myocytes, plays a major role in the generation of spontaneous activity and in the modulation of heart rate. Selective inhibition of the $I_f$ current by specific $f$-channel blockage with ivabradine, represents a viable and efficient means of reducing heart rate without significant cardiovascular side effects. This is particularly useful in patients with myocardial ischemia where reduced heart rate helps to prevent exertional angina and underlying ischemia and the ongoing exploration with ivabradine will likely contribute to define a broader clinical role for the specific $I_f$ inhibitors in both emergency and non-emergency cardiovascular medicine.

3. The pre-clinical results with $I_f$ current inhibition by ivabradine illustrate a rapid and sustained, dose-dependent reduction of heart rate at rest and during exercise without significant effects on atrioventricular conduction, left ventricular (LV) contraction-relaxation or vascular tissues. This suggests that the long-term heart rate reduction with ivabradine might play a role in the cardiac and vascular remodelling processes associated with chronic heart disease.

4. The clinical benefits of pure heart rate reduction to relieve ischemia are well documented. The ongoing clinical development programme (in which BEAUTIFUL plays a major role) regarding cardiovascular morbidity-mortality, has the potential to greatly extend the use of ivabradine in patients with coronary artery disease (CAD) and left ventricular dysfunction who already receive guideline recommended optimal preventive therapy.

5. The future perspectives for additional study of $I_f$ inhibition by ivabradine in cardiology, include the potential role in the treatment of atherosclerosis and its complications and congestive heart failure. Further clinical and mechanistic studies to clarify the pathophysiological background could define the role of pure heart rate reduction in the broad spectrum of cardiovascular interventions.