

European Society of Cardiology focus on heart rate and ivabradine, with expert South African comment

Heart rate now a risk factor for cardiovascular disease

SHIT echocardiographic study supports ivabradine's heart rate-lowering benefits

The need to accept heart rate as a causative risk factor which provokes adverse events in patients at risk, including those with heart failure, was evident from the results presented by the SHIT and CLARIFY trialists at the recent 2011 ESC congress in Paris.

While some clinicians had felt that the results of the SHIT trial published last year,¹ and earlier beta-blocker trials had made a strong case for heart rate being a risk factor rather than a marker of poorer prognosis, the vital element of demonstrating reversal of disease when the risk factor is knocked out of the ring, was missing.

The results of the prospective echocardiographic study on a subgroup of the heart failure patients in the SHIT trial² now suggest that left ventricular remodelling in heart failure can be modified by ivabradine, the novel, rate-lowering agent.

The echocardiographic study was undertaken in 411 patients participating in SHIT and it evaluated left ventricular function at both baseline and after eight months of ivabradine therapy. The primary endpoint was the change in left ventricular volume index between baseline and eight months.

The population in the echocardiography study mirrored the overall population of SHIT, mainly older Caucasian men with non-valvular heart failure in sinus rhythm. The study showed that ivabradine therapy lowered the left ventricular end-systolic volume index (LVESVI) by -7.0 ml/m^2 compared to no change in patients on standard background therapy for heart failure. Similarly, the left ventricular end-diastolic volume

index (LVEDVI) was also decreased by ivabradine by -7.9 ml/m^2 , whereas with placebo, the volumes were little changed.

The decrease in left ventricular volumes were associated with a significant increase in the ivabradine-treated group ($+2.4$ versus -0.1 ; $p < 0.001$) compared to the standard-care group. 'It is worth noting that the standard care in SHIT was good, with 90% of patients on RAAS inhibitors and beta-blockers. One-third of the patients were titrated to the target beta-blocker dose while 54% received 50% of targeted doses', Dr Karl Swedberg, Gothenburg, Sweden said.

'These changes show some reversal of the adverse cardiac remodelling in heart failure. In addition, the improvements in left ventricular systolic function occurred independently of beta-blocker use, aetiology of heart failure, whether ischaemic or non-ischaemic, and the baseline ejection fractions', study presenter Professor Jean-Claude Tardif from the Montreal Heart Institute Canada commented. He also indicated that, 'when these cardiac changes were related to heart rate, we found that greater decreases in heart rate were associated with greater increases in LVEF'.

These results provide a mechanistic and pathophysiological explanation for the results of SHIT, which enrolled 6500 patients in sinus rhythm, with moderate to severe chronic heart failure and a LVEF $< 35\%$. Treatment with ivabradine superimposed on standard background therapy for heart failure was associated with an 18% reduction in risk for the primary composite endpoint of cardiovascular death or hospitalisation for worsen-

ing heart failure ($p < 0.0001$) and a 26% reduction in heart failure deaths ($p = 0.014$).

A further interesting animal model study in diabetic mice presented at the ESC showed that ivabradine reduced vascular and left ventricle stiffness, thereby improving left ventricular contractility and diastolic functioning.³

Improving quality of life: a new evaluation within the SHIT study

A second SHIT analysis set out to assess whether quality of life in heart-failure patients was related to prognosis and changes in heart rate.⁴ It involved 1944 patients with chronic heart failure from 24 participating countries, with no biasing reason for exclusion, except where the relevant questionnaire was not available and standardised in the local languages.

Health-related quality of life was assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ), a validated, disease-specific measure of functional status and quality of life. The 23 items of the questionnaire are divided into two sets of scores, the clinical summary score assessing physical limitation and symptoms and the overall summary score assessing social limitations in chronic heart-failure patients. The higher the score, the better the quality of life.

By one year, the study showed that the risk of a cardiovascular event increased in patients with lower KCCQ scores (equating to a lower health-related quality of life). The reduction in heart rate achieved through treatment with ivabradine was associated with almost double the improvement in quality of life

compared to the control group. This improvement was observed in both the disease-related component and the social component of the scores. Practically speaking, this means that patients treated with ivabradine were able to participate in a greater number of everyday activities, considerably changing their day-to-day life.

Comments from South African experts

Prof Karen Sliwa, University of Cape Town

It is reassuring to have an explanation of ivabradine's action in terms of improved left ventricular function, reduction in left ventricular size and improvement in the contractility of the left ventricle. The data come from a thorough echocardiographic study of a sub-set of patients that was well matched to the profile of the heart-failure patients within the overall SHIT study.

The importance for the clinician is to underscore the opportunity to further improve outcomes in heart-failure patients who are receiving maximum ACE inhibition and beta-blocker therapy and yet have a heart rate above 70 beats per minute. While ivabradine is not yet widely used in the South African public sector, this new finding of reversal of disease progression could help to make a powerful case for its wider use; for example, in younger patients where longer-term benefits can accrue with significant cost savings in both hospitalisation and chronic care.

We should not be too concerned by the slow uptake around the world of this novel modality, including of course in South Africa. I was struck by the results of the PURE study, also released at this meeting by Dr Salim Yusuf, which has shown a huge under-use of cheap and proven drugs, such as the older antiplatelet agents, ACE inhibitors or ARBs and statins in the secondary prevention of cardiovascular disease.

This occurred in low-, middle- and high-income countries, with the low-income countries in the study (China, Columbia and Iran) showing the worst treatment coverage, with some 80% of their patients receiving no preventative medication. Even in high-income countries (Canada, Sweden and United Arab Emirates), some 12% of people were not being treated with these life-saving medications. In this study, which was set up in 2003 in 17 countries, South Africa was ranked with the middle-income countries of Argentina, Brazil, Malaysia, Poland and Turkey.

Prof DP Naidoo, KwaZulu-Natal

For me personally, the results from the initial SHIT study, published late last year, made a good case for heart rate reduction as a means to reduce cardiovascular risk. Today, with my understanding of ivabradine's underlying mechanism of action, I would place this therapy in a new category of 'a disease-modifying agent', which carries much more impetus for use.

For example, there are some clear opportunities emerging for improved care from the CLARIFY baseline data on coronary artery disease (CAD) to which South Africa has contributed more than 500 patients. [The CLARIFY (ProspeCtive observational Longitudinal Registry of patients with stable coronary artery disease) registry was designed to increase knowledge and understanding of CAD, including an assessment of the role that heart rate plays in the prognosis of CAD patients. Dr Naidoo is the South African co-ordinator for this registry.]

CLARIFY had already enrolled 33 649 patients worldwide between November 2009 and July 2010. The mean age of patients, 77.5% of whom were men, was 64 ± 11 years. Despite the fact that most of the patients were on beta-blocker therapy, 22% still experienced angina and more than a third had high heart rates. There

is therefore a clear need for further treatment of these patients with heart rate-lowering agents such as ivabradine to improve survival, and importantly, to improve quality of life.

Dr Shirley Middlemost, Hermanus, Western Cape

The extent of reversal of cardiac remodelling achieved with ivabradine is an important observation. With regard to standard heart-failure therapy, only beta-blockers and not ACE inhibitors have been able to significantly reduce left ventricular end-systolic volume index. An interesting finding was that not only was the end-systolic volume significantly reduced but the end-diastolic volume was also significantly reduced. In spite of these observations, the ejection fraction was significantly increased.

Clinicians now accept that heart rate is an important therapeutic target in both ischaemic heart disease and heart failure. In both entities we know that the target should be less than 70 beats per minute. Furthermore, current guidelines recommend a target of 55–60 beats per minute in stable coronary artery disease.

The Quality of Life sub-study in the SHIT population showed a significant improvement in quality of life, as determined by the Kansas City Cardiomyopathy Questionnaire (KCCQ). This is a significant finding in view of the fact that patients with moderate to severe heart failure have a quality of life similar to that of patients on haemodialysis. Neither ACE inhibitors nor beta-blockers have been shown to improve quality of life.

Prof Pinky Sareli, Johannesburg

Heart rate reduction is now clearly established as a cardiovascular risk factor. As clinicians, we can no longer leave this aspect untreated in our patients.

In question time after the ESC presentations, I asked 'What do we do

about patients with other conditions, presenting with raised heart rates; how should they be treated?' The SHIFT experts answered carefully that you would need to assess each patient individually and that each patient (if without atrial fibrillation) could be an own mini-study because ivabradine is so safe and easy to use.

Instinctively, I think about diastolic heart failure with preserved ejection fraction, acute decompensated heart failure due to all forms of car-

diomyopathies, diabetic patients with CAD, and raised heart rate due to autonomic dysfunction, also CAD patients who are obese with raised heart rate. We now have two classes of agents at our disposal to treat these patients and we should aim to get to the target heart rate of below 70 beats per minute.

1. Swedberg K, *et al.* Ivabradine and outcomes in chronic heart failure (SHIFT) – a randomised placebo controlled study. *Lancet* 2010. DOI: 10.1016/S0140-6736(10)61198-1.

2. Tardif J-C, *et al.* Effects of selective heart rate reduction with ivabradine on left ventricular remodeling and function: results from the SHIFT echocardiography substudy. *Eur Heart J*. Published online 29th August 2011.

3. Reil JC, *et al.* Selective heart rate reduction by ivabradine increases aortic distensibility as well as LV systolic and diastolic function in diabetic mice. ESC 2011, Poster 3557.

4. Ekman I, *et al.* Heart rate reduction with ivabradine and health-related quality of life in patients with chronic heart failure. Results from SHIFT. *Eur Heart J*. Published online 29 August 2011.