Kardiologia Polska 2013; 71, 6: 549–551; DOI: 10.5603/KP.2013.0117 ISSN 0022–9032

Novel approaches to heart rate modulation in chronic heart failure

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INTRODUCTION

The most recent version of the European Society of Cardiology (ESC) Guidelines for the management of heart failure (HF) has introduced two important innovations for the medical treatment of chronic HF with reduced ejection fraction (EF): mineralo-corticoid receptor antagonists (MCRA) and the If channel blocker ivabradine have now a recognised indication in patients remaining symptomatic despite diuretics, angiotensin converting enzyme inhibitors (or angiotensin receptor blockers in case of intolerance) and beta-blockers [1].

Mineralo-corticoid receptor antagonists are recommended following the EMPHASIS trial which demonstrated the benefit of eplerenone on cardiovascular mortality or HF hospitalisations as well as on all causes mortality in mild to moderate HF patients with reduced EF [2].

According to the ESC Guidelines, ivabradine should be considered when patients remain symptomatic despite the addition of a MCRA and when they have an increased heart rate (HR) ≥ 70 bpm in the context of sinus rhythm. This new recommendation derives from the results of the large outcome trial using this new agent, the SHIFT trial (Systolic Heart Failure Treatment with the If inhibitor Ivabradine trial) [3].

HEART RATE AND HEART FAILURE

Elevated HR is associated with poor outcomes in coronary artery disease and low EF and, in HF [4, 5] and HR reduction with beta-blockers, is associated with improved outcomes [6].

Surveys performed in real life populations consistently show that HR remains elevated in the majority of patients [7, 8]. This is probably due to the fact that (i) approximately 25% of patients do not tolerate beta-blockers and (ii) the proportion of patients reaching the beta-blocker dose recommended by international guidelines is also limited to one quarter.

Ivabradine is a specific inhibitor of the If current in the sino atrial node and is devoid of any other known action on the heart or on the cardiovascular system [9].

Ivabradine was tested in the SHIFT trial in order to evaluate whether the addition of this new agent on top of optimal HF therapy improves outcomes.

MAIN RESULTS FROM SHIFT

SHIFT randomised 6,558 patients of whom 6,505 were analysable. The main inclusion criteria were the following:

- age ≥ 18 years;
- sinus rhythm;
- resting HR ≥ 70 bpm measured on a 12 lead electrocardiography after at least 5 min rest on two consecutive visits before randomisation;
- stable symptomatic chronic HF;
- prior hospitalisation for worsening HF within the previous 12 months;
- left ventricular EF ≤ 35%.

Due to the mechanism of action of the drug, patients with atrial fibrillation or flutter and patients with a pacemaker operative ≥ 40% of the day were excluded.

Importantly, patients needed to be on optimal and stable background HF therapy and, in particular, the reasons for not providing/uptitrating beta-blockers were recorded for each patient.

Ivabradine was started 5 mg twice daily and increased to a target dose of 7.5 mg twice daily unless resting HR was ≤ 60 bpm. If resting HR was < 50 bpm during the titration period, or in case of signs or symptoms related to bradycardia, the dose was reduced to 2.5 mg twice daily.

The average age was 60.4 years; 76% of patients were male and mean HR was 80 bpm whereas mean EF was 29%.

A renin angiotensin blocker was used in 91% and a beta-blocker in 89%; 56% of the patients under beta-blocker received at least 50% of the target dose as defined by the ESC guidelines, and 26% were at target dose.

The addition of ivabradine to background therapy resulted in a marked HR reduction of 10.9 bpm placebo corrected at 28 days.

The primary composite endpoint, cardiovascular mortality or HF hospitalisation was reduced by 18% ($p < 0.001$)

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and the effect was driven mainly by hospital admissions for worsening HF which were reduced by 26% ($p < 0.001$).

Cardiovascular deaths were reduced by 9% (NS) whereas HF deaths were significantly reduced by 26%.

All measured endpoints tended to be improved in the active arm whether reaching statistical significance or not.

Various subgroup analyses were performed based on age, gender, aetiology of HF, severity of HF, and use/non use of beta-blockers. These analyses showed no significant variance in the benefit brought by ivabradine. However, the effect tended to be greater in patients with resting HR > 77 bpm (median value in the population) than in those with lower values.

The safety was excellent and 1% of patients had to be withdrawn from the trial for symptomatic or asymptomatic bradycardia. The number of patients withdrawn for visual side effects (phosphenes) was also very limited.

QUALITY OF LIFE AND HEART RATE

Heart failure is associated with a very poor quality of life. Since life-saving drugs used in this condition have little (angiotensin converting enzyme inhibitors) or no (beta-blockers) demonstrated benefit on health related quality of life, a large sub analysis was made on 1,944 patients enrolled in the SHIFT trial using a well validated instrument, the Kansas City Cardiomyopathy Questionnaire (KCCQ). KCCQ is a questionnaire which has been shown to be a reliable health status measure in this condition [10]. This tool has two distinct dimensions: a clinical summary score (CSS) which evaluates the disability directly related to the disease, and an overall summary score (OSS°) which includes also social limitation. Patients randomised to ivabradine experienced a significant improvement in the overall summary score by 2.4 points placebo corrected ($p < 0.001$) and of the clinical summary score by 1.8 points ($p = 0.02$) at 12 months. Interestingly, these changes were correlated to the change in HR and this relationship was found not only in the active arm but also in the placebo arm, suggesting therefore that HR and its change are associated with quality of life.

MECHANISM OF THE BENEFIT INDUCED BY IVABRADINE

Cardiac remodelling plays a central role in the pathophysiology of HF and of its progression, and there is evidence that mortality following various medical interventions is correlated with the short term effect on cardiac dimensions [11]. An echocardiographic sub-study including 411 patients suitable for analysis was performed using a central core laboratory at baseline and eight months after randomisation [12]. It was observed that ivabradine reduced significantly end systolic volume index by 7 mL/m^2 vs. 0.9 mL/m^2 in the placebo arm ($p < 0.001$) as well as the end diastolic volume index by 7.9 mL/m^2 vs. 1.8 mL/m^2 ($p = 0.002$) and increased significantly EF by 2.4 points. These changes were consistent in the pre-specified subgroups irrespective of EF, aetiology of HF or beta-blocker intake. This study provides grounds for the role of HR reduction with a drug devoid of any other known mechanism of action to reverse cardiac remodelling.

IS THE BENEFIT INDUCED BY IVABRADINE RELATED TO BETA-BLOCKER DOSE OR TO BASELINE HEART RATE?

An important clinical question raised by SHIFT is whether the clinical benefit observed with ivabradine is related to the beta-blocker dose or to the baseline HR. To answer this question, a substudy was made, grouping patients by quintiles of HR (from < 72 to > 87 bpm) and of beta-blocker dose at baseline (no beta-blocker to > 100% of the target dose) [13]. This analysis is complicated by the fact that there are confounding factors i.e. patients not receiving beta-blockers or at low dose are significantly more severe, older and have more pulmonary co-morbidities than those at full dose. However, it was observed that, although there was a nominal increase in the benefit on outcomes with ivabradine in patients at low/no doses of beta-blockers, the various statistical tests for interaction were not significant and, in particular, when these tests were adjusted for baseline HR, no difference was found. This study leads to the conclusion that the effect of ivabradine is driven by baseline HR and its reduction, and not by baseline beta-blocker dose.

EFFECT OF IVABRADINE IN PATIENTS RECEIVING MINERALO-CORTICOID RECEPTOR ANTAGONISTS

The publication of the EMPHASIS trial has highlighted the benefit brought by MCRA. In this context, it is important to evaluate whether ivabradine is beneficial on outcomes in patients receiving or not receiving this class of medication. This analysis was made possible since 60% of patients were under MCRA at baseline. It was, in almost all instances, spironolactone [14].

The first finding was that patients enrolled in SHIFT with MCRA were more severe and had a poorer outcome than those without MCRA: an analysis of the placebo arm showed that all outcomes were increased by 30–50% in patients receiving MCRA compared to those not under MCRA. The assessment of the effect of ivabradine on outcomes, in particular the primary composite endpoint, showed consistency in MCRA+ vs. MCRA– patients. These findings suggest therefore that these two classes of HF medication are complementary and that, in particular, patients under MCRA with increased HR > 70 bpm should be considered for the addition of ivabradine in order to further improve clinical outcomes.

EFFECT OF IVABRADINE ON RECURRENT HOSPITALISATIONS

Hospitalisations for worsening HF are lengthy and recurrent and they account for approximately two thirds of the overall

cost of the management of this condition. Reducing the burden of HF admissions is therefore of paramount importance in order to optimise the medical resources needed for the treatment of these patients. The SHIFT trial showed that the first occurrence of an HF admission was reduced by 18%. A secondary analysis was performed in order to assess the impact of this treatment on the overall number of admissions for HF and on recurrent hospitalisations [15]. It was observed that ivabradine reduced the total number of admissions for HF by 25% and that it also reduced significantly the occurrence of a second or a third admission for HF. This study demonstrates therefore that the benefit of ivabradine on a major outcome in HF is sustained. By reducing the overall burden of HF admissions, this drug reduces the costs related to this condition.

WHAT IS THE OPTIMAL HEART RATE IN HEART FAILURE?

The analysis of the rate of the primary outcome in SHIFT (cardiovascular mortality or HF hospitalisations) based on the HR achieved at 28 days after initiation of ivabradine demonstrates that the lowest incidence is observed in patients reaching a HR < 60 bpm and in those with the greatest reduction in HR [16]. From this observation, it can be assumed that a HR < 60 bpm should be sought in order to reduce cardiovascular risk as much as possible. There is no clear answer to the question of how low HR should be reduced. Cardiac output is the product of stroke volume by HR. Therefore, a very large reduction in HR might induce a significant cardiac output reduction and, hence, result in detrimental organ perfusion. It is therefore reasonable to propose an optimal range of 50 to 60 bpm.

CONCLUSIONS

Heart rate is a major risk marker in HF. Since HR reduction results in cardiovascular risk reduction, it can be assumed that HR is also a risk factor. There are currently two different pharmacological approaches to achieve HR reduction: beta-blockade and ivabradine. As stated by all international guidelines, beta-blockers should be considered in the first instance in HF with low EF. However this class of drug is often difficult to manage in real life due to contra-indications or side effects making up-titration challenging.

This explains why all contemporary surveys show that HR remains elevated in many patients in the era of beta-blockers. In patients intolerant to beta-blockers or unable to be up-titrated and in sinus rhythm, ivabradine should be considered in order to improve clinical outcomes, particularly HF hospitalisations, and quality of life when HR is increased > 70 bpm.

Conflict of interest: *MK is co-principal investigator of SHIFT and has recieved honoraria for this activity.*

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