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Expert group consensus regarding the place of ivabradine in therapy optimization in patients with chronic heart failure

Stanowisko grupy ekspertów dotyczące miejsca iwabradyny w optymalizacji terapii u chorych z przewlekłą niewydolnością serca

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Abstract

Accelerated heart rate is a risk factor of general and cardiovascular mortality in different populations. The classical treatment to achieve heart rate reduction by beta-blockers and calcium channel antagonists from the group of non-dihydropyridines (verapamil and diltiazem), is often limited by contraindications or adverse reactions. Ivabradine is a unique, modern drug which mechanism of action is blocking the I_f current in the sinoatrial node. This translates into a reduction in heart rate — a parameter associated with poor prognosis in patients with heart failure (HF). The following document contains the opinion of an expert group summarizing current knowledge on ivabradine and its use in population of patients with HF.

Key words: therapy optimization, heart failure, ivabradine

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Introduction

Heart failure (HF) is currently one of the most serious health problems in Poland. It is estimated that about one million people may suffer from HF in Poland, and the number of new cases is estimated at 220,000 per year [1]. Worldwide, HF is a global public health problem affecting 23 million people. In the United States, the prevalence of HF is estimated at 5.7 million [2]. Among the countries represented in the European Society of Cardiology (ESC), the number of patients with HF is about 15 million [3].

Considering that HR is caused by pathologies such as coronary artery disease, hypertension, diabetes mellitus or obesity, as well as by the growing population of elderly people, it can be concluded that there will be a significant increase in patients with heart failure. The risk of HR in the European population at the age of 55 is 33% for men and 29% for women, after the age of 85 it equals 17.4% for both sexes [4, 5].

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Despite the significant progress in medicine, the prognosis in HF is still serious. In 5 years post diagnosis 60% of men and 40% of women die. Mortality of the entire population of patients with HF, regardless of etiology, is about 10% per year. The number of patients with this disease is 2.5 times higher than the number of patients with all cancers combined. Every day 117 Poles die of HF, which means 43,000 deaths per year [6]. Half of the patients die within 5 years of the diagnosis of the disease. These statistics are significantly worse than in the case of breast, ovarian or prostate cancer. Therefore, every effort should be made to improve the prognosis by comprehensive, up to date treatment.

Hospitalization in HR — economic aspects

The annual costs of treatment of patients with HF in Poland increased to 1.7 billion PLN and already account for 3.2% of the National Health Fund (NFZ) budget [1]. According to the data of the Institute of Health Care Management, in 2009 all diagnoses within HF constituted 7.17% of total hospitalization among women over 65 years of age and 6.77% among men over 65 years of age [7]. In 2012, the National Health Fund financed services for patients treated for HF spending over 672 million PLN [7]. The largest amount was spent on hospital services — 635 million PLN (94%), followed by therapeutic rehabilitation — 26 million PLN (4%) and outpatient specialist care — 10 million PLN (2%). The share of these costs in the total provision was 2.2% in the case of hospital treatment, 1. 3% in the case of rehabilitation and 0. 2% in the case of outpatient specialist care [7].

Heart failure is the most common cause of hospitalization among people over 65 years of age. In 2012, the NHF accounted for the treatment of this disease in the group of 288,000 patients in total, 158,000 of whom were over 69 years of age [7]. Emergency admissions concerned almost 83% of the total number of admissions. In 2012 in Poland 187,000 patients were admitted to hospital for HF and every fourth patient was hospitalized again in less than 30 days after discharge.

Poland was ranked first among 30 Organization for Economic Co-operation and Development (OECD) countries in terms of the number of hospitalizations due to HF, being ahead of the United States, Germany and Austria [8]. The number of hospitalizations in our country is twice as high as the OECD average. In 2012, the costs related to hospitalization of 187,500 patients amounted to PLN 635 million, which gives an average of about PLN 3,400 per year per patient. The mean period of hospitalization of patients with HF (group E53; HF in patients > 69-years-old or with complications and coexisting diseases) in Poland in 2012 was 6 days (median) [7]. It is estimated that with an increase in the number of patients with HF by 25% over the next 20 years, the associated treatment costs will increase twice.

Optimal heart rate — the aim of cardiac therapy

Accelerated heart rate (HR, heart rate) is one of the basic and early symptoms of HF. It correlates with the severity of the disease regardless of its etiology, being a recognized symptom of prognostic value. Only acceleration of heart rate, if it is significant and lasts long enough, may worsen the contractility and become the sole cause of HF. This condition is defined by tachyarrhythmic cardiomyopathy, which according to the current classification belongs to the group of primary acquired cardiomyopathies [9]. Tachycardia is also a recognized disrupter of the ventricular inflow and exacerbates symptoms of diastolic dysfunction or heart failure with preserved ejection fraction (HFpEF). Ischemia provoked by insufficiently controlled HR can lead to myocardial hibernation and reversible deterioration of ventricular systolic function.

According to numerous studies, both cardiovascular mortality and total mortality in patients with HF are directly proportional to HR.

Key data defining HR ≥ 70 bpm associated with poorer prognosis obtained in the BEAUTIFUL study which involved typically treated population with ischemic left ventricular dysfunction. What is extremely important — a decrease in HR allows to reduce mortality. This has become the basis for the use of drugs, thanks to which HR is a parameter which is relatively easy to modify influencing the prognosis in HF.

The results of numerous clinical trials have confirmed the high therapeutic efficacy of decrease in HR in HF — initially achieved only with beta-adrenolytic drugs. HR change is not the only element of beta-adrenolytic action — apart from chronotropically negative effect, the effect of blocking the activation of adrenergic system causes reduction of dangerous cardiac arrhythmias, reduction of ischemia and post-infarction myocardial damage and counteracts left ventricular remodeling. HR achieved during treatment is also a good indicator of its effectiveness. Meta-analysis of McAlister and his team based on data from 23 studies on systolic HF showed that the degree of HR decrease, rather than the dose of beta-adrenolytic, correlates with clinical benefits. With an average 24% reduction in mortality across the group, HR decrease of 5 bpm (but not reaching a specific dose of the drug) was shown to reduce mortality by 18% [10]. This strong evidence of reduced mortality in patients with HF in NYHA class II–IV and reduced risk of other key complications makes beta-adrenolytics the first line of treatment in systolic HF and is recommended together with angiotensin-converting enzyme (ACE) inhibitors in all patients with left ventricular ejection fraction (LVEF)

< 40% in order to reduce the frequency of hospitalization due to HF and the risk of premature mortality. Importantly, the recommendations do not recognize the class effect and apply to drugs tested in prospective clinical trials – metoprolol extended-release, bisoprolol, carvedilol and — despite the lack of full evidence of reduced overall mortality — nebivolol.

However, the common use of beta-adrenolytics is associated with the risk of adverse effects, common in patients with HF. This is the main reason for under-dosing or not including this group of drugs to the treatment regimen, despite the obvious benefits. Among the most common causes are hypotonia, exacerbation of intermittent claudication or bronchospastic symptoms. In a certain percentage of cases, the use of beta-adrenolytics, even at the right dose, is expressed by deterioration of respiratory parameters. Although $beta_2$ receptors dominate in the smooth muscles of the bronchial tree, it is estimated that the percentage of $beta_1$ receptors reaches 20% and therefore the use of $beta_1$ selective preparations may cause exacerbation of asthma and chronic obstructive pulmonary disease. This leads to a confirmed therapeutic gap — only 22% of Polish patients with HF take the optimal dose of beta-adrenolytic, and 23% do not receive it at all [11]. Also, data from the DATA HELP register indicate that HR median of Polish patients with HF exceeds 70 bpm [12, 13]

Undoubtedly, the most sensitive period after discharge are the first few weeks, when the risk of death and re-hospitalization due to HF is the highest [14]. Studies show that in both cases the risk was highest within one month of discharge and then it gradually decreased, especially in respect to deaths due to progress of HF and sudden cardiac death.

The longer the patient has been hospitalized, the higher the risk of death (which is probably associated with more advanced HF) and the more hospitalizations he has experienced in the past. Unfortunately, a significant number of patients discharged from the hospital after HF exacerbation still have an increased heart rate [15].

Out of the group evaluated in the OPTIMIZE-HF register, only 73% of individuals discharged from the hospital were treated with beta-adrenolitics. In patients without beta-adrenolytic therapy, HR median was 80 bpm (IQR 70–89 bpm), in comparison to HR 78 bpm (IQR 69–88 bpm) in patients with < 25% target dose, HR 74 bpm (IQR 66–82 bpm) in patients with 25–49% target dose, HR bpm (IQR bpm) in 55–99% target dose and HR of 72 bpm (IQR 65–80 bpm) in patients in whom the 100% target dose of beta-adrenolytic acid has been reached. Data from this register show that 71% of patients are discharged from the hospital with a heart rate ≥ 70 bpm, 63% of whom are discharged with ≥ 50% of the target dose of beta-adrenolytic acid. Unfortunately, which was also confirmed in the OPTIMIZE-HF register, further optimization of the dose of beta-adrenolytic drugs in ambulatory conditions does not take place. According to the data from the cited register, after 60 and 90 days after discharge 70–75% of patients (depending on the type of beta-adrenolytic therapy) took the same dose of the drug prescribed when discharged from the hospital, and in 9–13% of patients the dose was reduced in relation to the discharge. Only in about 15% of cases an attempt was made to increase and further optimize beta-adrenolytic treatment. After 60 and 90 days after discharge, only 17.5% and 7.9% of patients were treated with the target dose of beta-adrenolytic, respectively [16]. Therefore, especially those who have been hospitalized due to HF should receive optimal treatment at the time of discharge to modify the further course of the disease, including a correspondingly reduced heart rate. Any re-hospitalization may indicate the ineffectiveness of the current treatment scheme/strategy and repeating it without changes (including adequate modification of heart rate) does not guarantee that re-hospitalization will not be avoided.

The QUALIFY registry, which is an international prospective observational study of 7,092 patients with HF who have been hospitalized for HF in the period of 1–15 months prior to including them into the study. The study analyzed how many patients, after discharge from the hospital, follow the recommendations for the use of ACE inhibitors, beta-adrenolytics, sartans, aldosterone and ivabradine antagonists. The results showed that 67% of patients follow the recommendations in a good level, 25% as moderate level and 8% in bad level. According to Polish QUALIFY registry data, for ACE inhibitors only 27% of outpatient patients reached the target dose, for sartans — 4%, beta-adrenolytics — 17.7%, and for aldosterone antagonists — 66% [17]. Compared to global data, Polish patients of the QUALIFY registry are more often treated with the recommended standard drug groups (ACE inhibitors/ /sartans, beta-adrenolitics and aldosterone antagonists) except for ivabradine (33% baseline results in the world vs. 13.9% in Poland) [17]. Every third patient in the world is treated with ivabradine, whereas in Poland it is used in every seventh outpatient patient with HF, although 25% of the Polish population of the QUALIFY registry had a sinus rhythm with a frequency greater than or equal to 75 bpm [17]. Moreover, only 39.2% of patients achieved a resting heart rate below 70 bpm.

These data show that in Poland we do not make use of the possibilities of optimizing the therapy of patients with HF in the context of the possibility of decreasing the heart rate. They also prove that using all recommended therapies in everyday practice, including ivabradine, is the only way for further improving the prognosis in this difficult group of patients. It is also worth emphasizing that ivabradine dosage is not complicated, it requires rhythm

analysis in electrocardiogram and heart rate control in order to determine the dosage. This should be performed by a GP or a cardiologist working in an out-patient clinic.

Ivabradine — drug characteristics

Pharmacological action of the drug

Ivabradine belongs to a new class of drugs that selectively slow down heart rate. The mechanism of its action is a selective and specific inhibition of the ionic current in the sinus node cells [18]. They are part of a group of pacemaker cells, which have the ability to spontaneously generate action potentials. Four types of membrane channels and the ionic currents flowing through them, including the pacemaker current flowing through a channel takes part in the automatic mechanism of pacemaker cells. Channel f belongs to the family of ionic HCN channels (hyperpolarization-activated cyclic nucleotide-gated channel), presence of which was found only in the heart, in some parts of the brain and in the retina of the eye. The fact that the occurrence of the current If is initiated by hyperpolarization, makes it so unusual that when it was detected in 1979, it was called funny. Until then, it was believed that ion channels in myocardial cells were only activated by depolarization of the cell membrane [19].

Channels f are also directly activated by molecules of cyclic adenosine-3'-5'-monophosphate (cAMP), which are inside the cells. Stimulation of beta-adrenergic receptors leads to activation of adenylate cyclase, which causes an increase in cAMP concentration, which leads to activation of the If current, shortening of depolarization diastolic time, shortening of the diastolic phase and acceleration of heart rate [4, 20, 21].

Thus, as a result of blocking the f canal, resting depolarization of the sinus node during the period of diastole occurs, as a result the heart rate slows down. Ivabradine acts exclusively on the sinus node and does not affect the conduction time in the atrium, atrioventricular node or ventricles, nor does it affect the contractility of the heart muscle (except for effects caused by slowing down heart rate) or ventricular repolarization. It is commonly believed that it also has insignificant and clinically irrelevant influence on blood pressure [22, 23].

Although no significant influence of ivabradine on the duration of the corrected QT or PR interval has been observed in preclinical studies [24], in some people, the use of ivabradine and associated slow heart rate may increase the prolongation of the QT interval. Therefore, caution should be exercised or the use of ivabradine should be avoided in patients with long QT syndrome or those taking drugs that prolong the QT interval [23].

The selective action of ivabradine on the sinus node is a unique feature among drugs used to slow down heart rate. Other substances, including beta-adrenolitics, nondihydropyridine calcium channel blockers (verapamil and diltiazem), amiodarone or digoxin, have a hypotensive effect they reduce myocardial contractility and have pro-arrhythmic effects, which in patients with HR is a significant limitation of their use [13].

In the recommended doses ivabradine slows down the heart rate at rest and during exercise by about 10 bpm. Its blocking power increases with heart rate, so the higher the heart rate before treatment, the greater the therapeutic effect [18]. This drug increases the ejection heart volume, which means that the minute capacity of the heart remains unchanged when it is slowed down. This is a distinguishing feature of ivabradine from beta-adrenolitics, which by reducing heart contractility leads to a decrease in its ejection and minute capacity [25, 26]. Although the f-channels are also present in the lower parts of the myocardium, they remain inactive under physiological conditions, so ivabradine reduces the heart rate only in patients with sinus rhythm [25]. It is worth emphasizing that ivabradine has the ability to bind to channel f only when it is open. Therefore, it connects more effectively to its place of bonding when the cycles of closing and opening of the f canal occur quickly, *i.e.* — as mentioned above — when the heart rate is higher. On the other hand, thanks to this property, the slower the HR is, the less effective the drug is, and as a result the risk of severe bradycardia is reduced [27].

Pharmacokinetics and pharmacodynamics

After oral administration, ivabradine is quickly and almost completely absorbed from the gastrointestinal tract. T_{max} when administered in fasting state is 1 hour. Due to the effect of the first passage in the intestines and liver, bioavailability is about 40%. Food delays drug absorption by nearly 1 hour and increases the exposure on it in the plasma by 20–30%. Ivabradine binds to plasma proteins in about 70%. It is metabolized in the liver and intestines by oxidation exclusively by the cytochromes P-450, CYP3A4 isoenzyme. The main active metabolite is the N-demethyl derivative. Exposure to this substance corresponds to approximately 40% of exposure to the parent substance. Metabolism of this active metabolite also occurs with the isoenzyme CYP3A4. Ivabradine has a low affinity to CYP3A4, has no clinically significant stimulant or inhibitory effect on this isoenzyme and is therefore considered unlikely to affect the metabolism of other substrates or plasma concentrations of these substances. Conversely, CYP3A4 potent inhibitors or stimulants may have a significant effect on plasma ivabradine concentrations. $T_{1/2}$ in the elimination phase is 2 h, and the effective $t_{1/2}$ is 11 h. Metabolites are excreted at a similar percentage with feces and urine; about 4% of the dose is excreted with urine in the unchanged form. Elderly age and renal dysfunction do not affect the pharmacokinetics of the drug. In patients with moderate hepatic impairment, concentrations of ivabradine and its main metabolite are about 20% higher

than in patients with normal liver function. The drug is contraindicated during pregnancy and breastfeeding, and women of childbearing age must use effective methods of contraception during therapy [23]. It is also possible to administer ivabradine intravenously, but currently there is no parenteral form of this drug [28].

Indications

Since 2005 ivabradine has been used in the symptomatic treatment of chronic stable angina pectoris in patients with ischemic heart disease and normal sinus rhythm. It is recommended in patients with intolerance or with contraindications for the use of beta-adrenolitics.

Since 2009, following the ASSOCIATE study, it has been allowed to be used in combination with beta-adrenolytics in individuals who have not been adequately controlled with an optimal dose of beta-adrenolytic and whose heart rate is higher than 70 ppm.

In February 2012, following the announcement of the SHIFT results, another indication appeared in the form of chronic HR in class II–IV according to the NYHA classification, with systolic dysfunction, in patients with sinus rhythm, with a heart rate of ≥ 75 bpm, in combination with standard treatment, including beta-adrenolytic treatment, or when beta-adrenolytic treatment is contraindicated or not tolerated [23].

Adverse effects

Ivabradine is considered safe, rarely causes side effects, and if they occur, they are usually harmless. The most common are visual impairment (may affect about 14.5% of treated patients), described as transient sensations of strong light in part of the field of vision (usually caused by sudden changes in light intensity; they usually occur during the first 2 months of treatment). Slightly less (1–10% of patients) frequent are: blurred vision, bradycardia (especially in the first 2–3 months, including 0.5% of patients with severe bradycardia < 40 thighs per minute), 1st degree atrioventricular block, ventricular extrasystoles, headaches (mainly in the first month of treatment), dizziness (probably related to bradycardia) and additional atrial extrasystoles. Due to the ability of ivabradine to bind to channel f only when it is open, *i.e.* as a result of weaker action at a slower heart rate, as described above, the heart rate cannot be decreased by more than 18–20% of its initial value [27, 29]. An additional protection is the fact that when ivabradine is used at a dose of 20 mg twice daily, its action initially increases and then reaches the plateau [23].

Interactions

Ivabradine is metabolized exclusively by the cytochromes P-450, CYP3A4 isoenzyme and is a very weak inhibitor of this isoenzyme, so it does not affect the metabolism of other CYP3A4 substrates and their plasma concentrations. However, it should be remembered that CYP3A4 inhibitors increase plasma concentrations of ivabradine, while substances stimulating this isoenzyme decrease these concentrations. Increased plasma concentrations of ivabradine may cause a risk of severe bradycardia. Therefore, parallel use of ivabradine with strong CYP3A4 inhibitors, such as: azole antifungal agents (fluconazole, itraconazole, ketoconazole), macrolide antibiotics (erythromycin, josamycin, clarithromycin, telithromycin), HIV protease inhibitors (nelfinavir, ritonavir) and nefazodone is contraindicated. Strong CYP3A4 inhibitors such as ketoconazole (200 mg/24 h) and josamycin (1 g 2 ×/24 h) increase the mean plasma exposure to ivabradine by 7–8 times. Parallel use of ivabradine with QT prolonging drugs, *e.g.* quinidine, disopyramide, bepridil, sotalol, ibutilide, amiodarone, pimozide, ziprasidone, sertindole, mefloquine, halofantrine, pentamidine, cisapride, erythromycin intravenous (i.v.) is not recommended. If this association is necessary, the heart function should be closely monitored. The combination of ivabradine with diltiazem or verapamil resulted in an increase in plasma concentrations and an additional reduction in heart rate of 5 bpm, so it is not recommended to use these drugs in parallel. The consumption of grapefruit juice during treatment with ivabradine doubles its power, so its consumption during treatment should be reduced. CYP3A4 stimulants, including rifampicin, barbiturates, phenytoin and St. John's wort preparations, may reduce plasma concentrations of ivabradine and thus impair its effect [23].

Site and dosage of ivabradine in chronic heart failure

Since 2012, we can use a new drug with a unique effect, thanks to which, according to the results of the SHIFT study, it is possible to reduce the risk of hospitalization of patients with HR by 26% and to reduce the risk of death due to HR by as much as 26% [30, 31]. Treatment with ivabradine should be initiated in individuals with stable HR who, despite standard treatment (*i.e.* ACE inhibitor or angiotensin II receptor antagonist in case of intolerance of the 1st one, beta-adrenolytic and mineralocorticoid receptor antagonist) we may observe maintained symptoms of class II–IV in NYHA, LVEF ≤ 35%, the patient has a sinus rhythm and a HR of ≥ 70 bpm (Figure 1) [32]. The administration of ivabradine in the above mentioned group of patients may also be considered in patients intolerant to beta-adrenolytics [32].

Looking at the algorithm shown in Figure 1, it is worth suggesting the following practical advice:

- priority for CRT usage should be given to patients with left bundle branch block and QRS > 150 ms (this group uses this form of therapy the most);
- priority for usage of ivabradine should be given to patients with sinus rhythm and HR ≥ 75 ppm despite

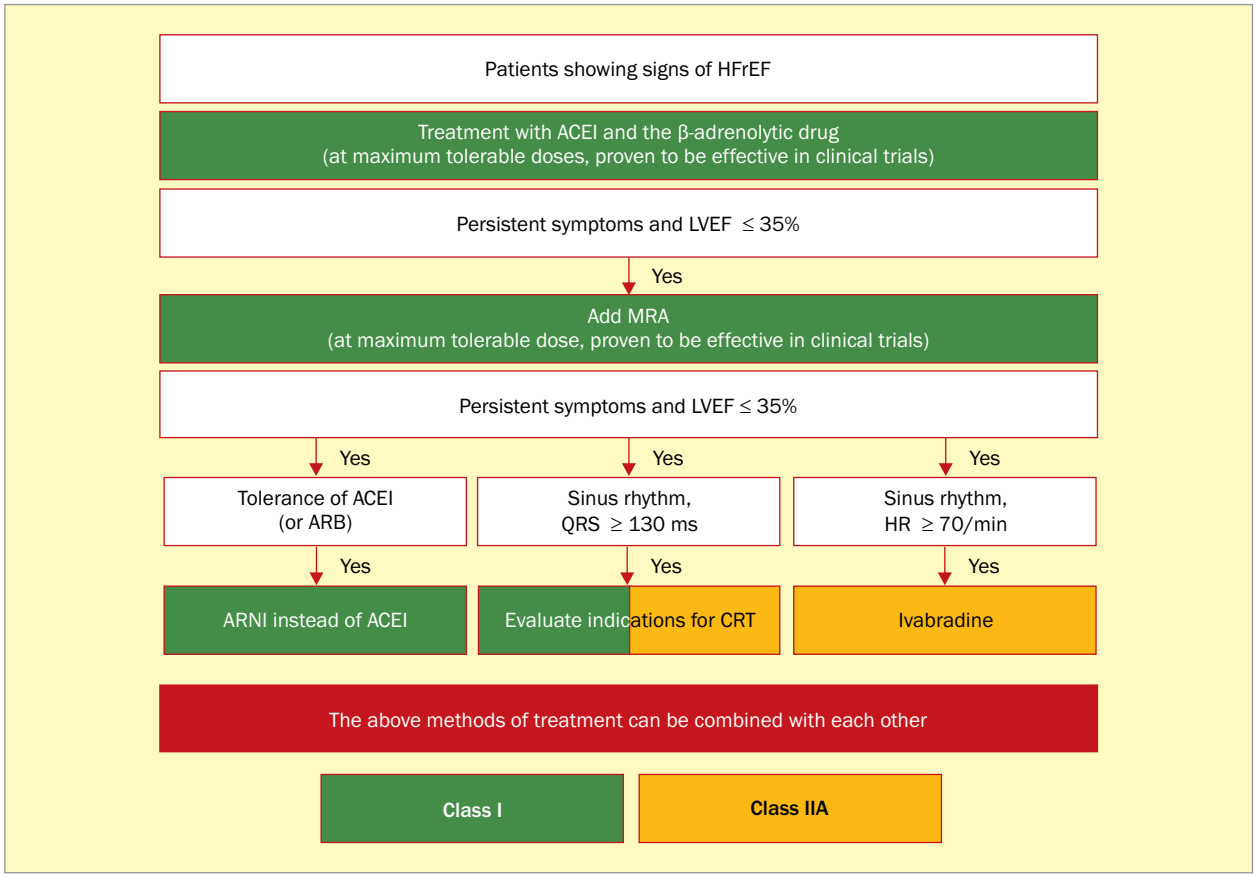

Figure 1. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure from 2016 — a part of the heart failure with reduced left ventricular ejection fraction (HFrEF) therapy algorithm — has been modified on the basis of (according to [32]); ACEI — angiotensin-converting enzyme inhibitor; LVEF — left ventricular ejection fraction; MRA — mineralocorticoid receptor antagonist/aldosterone antagonist; ARB — angiotensin II receptor antagonist /sartan; QRS — QRS complex width in electrocardiographic recording; HR — heart rate; ARNI — angiotensin receptor-neprilysin inhibitor; CRT — cardiac resynchronization therapy

the optimal dose of beta-adrenolytic or in case of intolerance or in case of contraindication for its usage;

— priority for introducing ARNI instead of ACE inhibitors used till now should be given to patients still showing symptoms of LVEF ≤ 35% and elevated natriuretic peptide levels (BNP ≥ 150 pg/ml or NT-pro-BNP ≥ 600 pg/ml).

It is worth remembering, that all three management procedures can be freely combined.

At this point, a certain inaccuracy should be noted. In the registration of the European Medicines Agency (EMA) and thus in the summary of product characteristics, the indication for the including of ivabradine is a HR ≥ 75 bpm, whereas according to the guidelines of the European Society of Cardiology, this HR limit is ≥ 70 ppm. The results of the SHIFT subanalysis showed a significant benefit of including ivabradine in a subgroup of patients with resting pulse rate ≥ 75 bpm that is why these differences have shown up. However, it is expected that these indications will be harmonized [23, 32].

Treatment with ivabradine (Figure 2) usually starts with a dose of 5 mg 2 ×/24 h, after 2 weeks the dose can be increased to 7.5 mg 2 ×/24 h if the resting HR is consistently > 60 bpm, or reduced to 2.5 mg 2 ×/24 h (1/2 of 5 mg tablets 2 ×/24 h) if subjective bradycardia symptoms occur or if the HR decreases for a long time < 50 ppm. When HR is 50–60 ppm, a dose of 5 mg 2 ×/24 h should be maintained. If during treatment, the HR at rest decreases permanently to < 50 bpm or if symptoms related to bradycardia appear, then in patients receiving a dose of 7.5 mg 2 ×/24 h or 5 mg 2 ×/24 h the dose should be reduced.

If the resting HR increases permanently to >60 bpm, patients receiving 2.5 mg 2 ×/24 h or 5 mg 2 ×/24 h may have their dose increased. Treatment should be discontinued if HR remains below 50 ppm or symptoms of bradycardia persist. In the elderly, an initial dose of 2.5 mg 2 × 24 h should be considered. It is not necessary to modify the dosage in patients with creatinine clearance of > 15 ml/min. People with creatinine clearance of

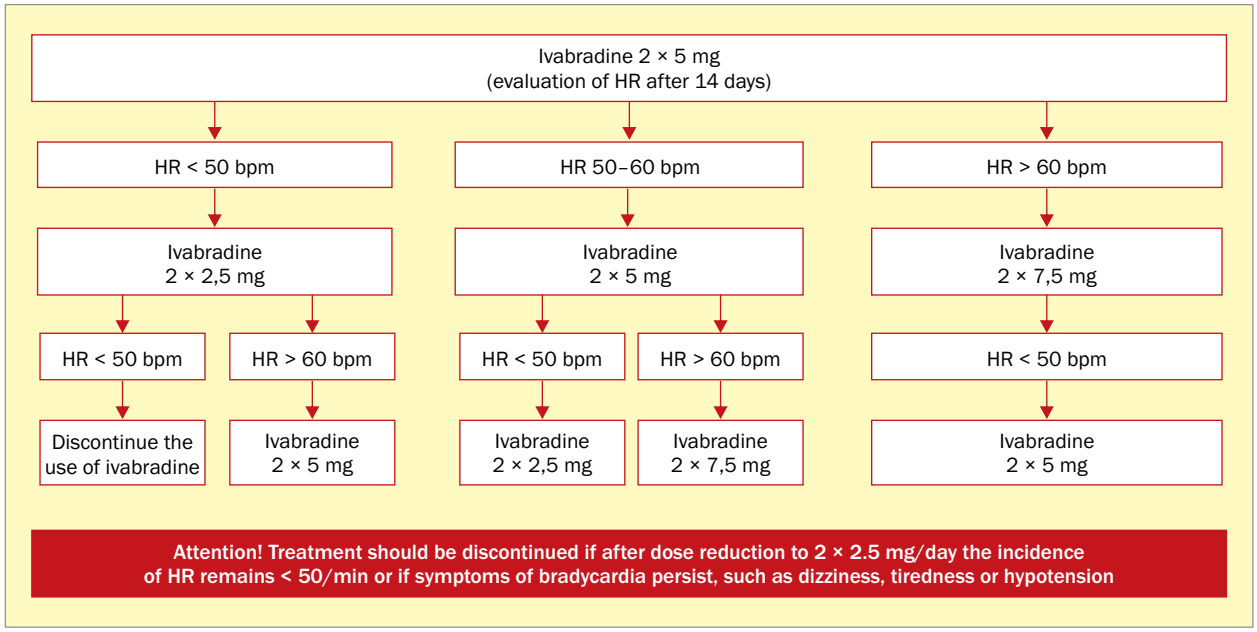

Figure 2. Dosage pattern of ivabradine in patients with heart failure (based on [25]); HR — heart rate

< 15 ml/min should be particularly cautious as there are no data on the safety of ivabradine in this group of patients.

There is no need to modify the dosage in patients with mild hepatic impairment, while in case of moderate disorders, caution should be paid [23].

The possibility of ivabradine use is of particular interest in patients in whom beta-adrenolytics should be avoided (in the case of 1st degree atrioventricular conduction block, peripheral vascular disease, bronchial asthma or severe chronic obstructive pulmonary disease). Unlike beta-adrenolytics, ivabradine can also be used in vasoconstrictive forms of angina, as it does not disturb the vasomotor balance of coronary vessels. Ivabradine also seems to be an important therapeutic option in patients receiving beta-adrenergic agonists with subsequent tachycardia, in middle-aged men who are particularly affected by potential sexual dysfunctions after the use of beta-block and in older patients with prolonged PR interval.

Studies with ivabradine

BEAUTIFUL study

The results of the BEAUTIFUL study were published in 2008–2009. This study was intended to assess the effect of ivabradine added to the standard treatment of ischemic heart disease on mortality and morbidity from cardiovascular causes. This was the first study with ivabradine with such large number of patients, involving more than 10,000 patients with documented stable coronary artery disease, left ventricular systolic dysfunction (with ejection fraction < 40% and left ventricular end-diastolic dimension in the short axis > 56 mm) and resting sinus rhythm > 60 bpm. The primary complex endpoint included death caused by cardiovascular reasons and hospital treatment for acute myocardial infarction and new or acute heart failure. In addition, secondary endpoints included, total mortality, mortality due to ischemic heart disease and heart failure, and hospitalizations due to ischemic heart disease, HR or the need for revascularization. The study showed no difference in the prevalence of the primary complex endpoint in the ivabradine-treated group compared to the placebo-treated group. However, in patients with HR ≥ 70 bpm, ivabradine significantly reduced the risk of myocardial infarction — by 36% ($p < 0.001$) and the risk of coronary revascularization — by 30% ($p = 0.016$) [33].

The analysis of patients with standard treatment (control group) showed that HR ≥ 70 bpm significantly increased the risk of cardiovascular death by 34% ($p = 0.0041$), hospitalization caused by HF by 53% ($p < 0.001$), hospitalization cause by myocardial infarction by 46% ($p = 0.0066$) and coronary revascularization by 38% ($p = 0.037$). The increase in resting HR by every 5 bpm increased the risk of cardiovascular death by 8% ($p = 0.0005$), hospitalization cause by HF by 16% ($p < 0.001$), hospitalization for myocardial infarction by 7% ($p = 0.052$) and coronary revascularization by 8% ($p = 0.034$). These results suggest that the risk of death and HF-related endpoint incidence increases continuously when HR > 70 bpm, while this relationship is less visible for coronary endpoints [34].

ASSOCIATE Study

The ASSOCIATE study showed that the combination of ivabradine and atenolol, has an additional anti-angina effect and improves the parameters of treadmill exercise test, without affecting the tolerance and safety of treatment. The study involved 889 patients with chronic stable coronary artery disease, receiving atenolol 50 mg/24 h, randomized to the group receiving 5 mg ivabradine, followed by 7.5 mg twice daily or a suitable placebo. The participants were tested three times: in the beginning, after 2 and 4 months of therapy. After 4 months in ivabradine group a significant increase in total exercise duration was observed (24.3 ± 65.3 s in ivabradine group when compared to 7.7 ± 63.8 s in placebo group; $p < 0.001$), time to decrease ST segment by 1 mm (45.7 ± 93 s in ivabradine group compared to 15.4 ± 86.6 s in placebo group; $p < 0.001$) and the time to development of signs of angina (49.1 ± 83.3 s and 22.7 ± 79.1 s, respectively; $p < 0.001$) [35]. The results of this study and the results of the BEAUTIFUL study were the green light for the simultaneous use of beta-adrenolitics with ivabradine.

SHIFT study

It is known that increased HR is associated with worse prognosis in many cardiovascular diseases, including heart failure, and sometimes it is difficult to decrease the HR in many of these patients despite the use of beta-adrenolytics. The authors of the SHIFT study asked themselves whether adding ivabradine to the standard treatment of HR could reduce the number of hospitalizations of these patients [31].

All cardiologists have known the answer to this question since 2010. After 23 months of observation, a significant (18%) reduction in the prevalence of the main endpoint, which consisted of cardiovascular causes of death and hospitalization due to decompensation of heart failure, was observed. Benefits were observed in practically all prospectively defined subgroups of patients. According to the analysis of individual components of the main endpoint, ivabradine reduces the risk of cardiovascular death by 9% (statistically insignificant difference) and reduces the risk of hospitalization due to decompensation of HR by 26% ($p < 0.0001$) [31].

The observation from the echocardiographic subanalysis of the SHIFT study is interesting, in which it turned out that ivabradine affects the remodeling and function of the left ventricular muscle. In the group of patients treated with ivabradine compared to placebo patients, a decrease in the left ventricular end-systolic volume index (LVESVI) by 7 ± 16.3 was observed vs. 0.9 ± 17.1 ml/m^2 ($p < 0.001$), reduction of left ventricular end-diastolic volume index (LVEDVI) by 7.9 ± 18.9 vs. 1.8 ± 19 ml/m^2 ($p = 0.002$) and increase of LVEF by 2.4 ± 7.7 vs. 0.1 ± 8% ($p < 0.001$) [36].

At the beginning of this claim, the importance of an ageing population and the prognosis of an increasing number of patients with HR has been highlighted. Given that hospitalization is one of the strongest independent prognosis factors in heart failure, it worsens the quality of life, and from an economic point of view represents the most important part of the costs associated with treating heart failure. The reduction in the risk of hospitalization by more than 25% as a result of using ivabradine in the SHIFT study has been noted, and thus in clinical practice, it is of particular value.

SIGNIFY Study

The results of the study, which were announced in September 2014, were intended to assess whether the use of ivabradine and thus the reduction in HR would have an impact on the reduced morbidity and mortality in patients with stable coronary artery disease, with preserved left ventricular function and no clinical signs of heart failure.

The study involved 19 102 patients from over 1139 centers. Patients aged ≥ 55 years, with stable coronary artery disease, LVEF > 40%, with sinus rhythm of ≥ 70 bpm and at least one risk factor of coronary artery disease were included to the study. Patients were randomly assigned to the ivabradine group (9550 people) at a dose adjusted to achieve a resting HR of 55–60 bpm [(but the dose couldn't exceed 10 mg/24 h (a dose of 2 × 10 mg was not yet registered for use)] and to the placebo group [37].

Ivabradine decreased the resting HR by 10 beats per minute (9.7/min; 95% CI). However, over a period of almost 28 months of observation, there were no differences in the incidence of a complex endpoint defined as cardiovascular death or non-fatal myocardial infarction between the two groups [6.8% (ivabradine) vs. 6.4% (placebo); $p = 0.20$; hazard ratio = 1.08].

SIGNIFY study results will not change the role of ivabradine in the therapy of heart failure, as the study applied to a different population of patients.

Everyone should be cautious and use their common sense when trying to pursuit the optimal HR, whereas the lower range of which is still unknown. As we know from experience, the golden mean is always the best.

ETHIC-AHF study

Increased HR is a disadvantageous prognostic factor when discharging a patient with heart failure. In some patients still in the hospital it may be useful to add ivabradine to the treatment with beta-adrenolytic. This type of strategy seems to be beneficial for patients with sinus rhythm and HR of ≥ 70 bpm, hospitalized once again due to HF exacerbation. Rehospitalization indicates that the current treatment strategy was ineffective and does not help us in avoiding of another rehospitalization without the modification of the therapy.

The aim of the ETHIC-AHF study was to evaluate the effect of early concomitant use of ivabradine (2 × 5–7.5 mg)

with beta-adrenolytic (bisoprolol or carvedilol) in comparison with monotherapy of beta-adrenolytic at the optimal dose (bisoprolol — 10 mg/day, carvedilol 50 mg/day) or at the maximum tolerated dose — control group, in patients with heart failure with reduced ejection fraction.

The authors analyzed the annual results of observations comparing these two treatment strategies in patients with sinus rhythm and HR of > 70 bpm [38].

71 patients were qualified for the study (33 in the study group and 38 in the control group). After 28 days the HR was lower in the study group (64.3 ± 7.5 vs. 70.3 ± 9.3 bpm, p = 0.01), and this difference persisted also after one year of therapy (61.8 ± 5.5 vs. 68.4 ± 9.3 bpm, p = 0.01). Doses of beta-adrenolytics were similar in both groups [38].

Left ventricular ejection fraction was significantly higher in the study group (48.2 ± 17 vs. 41.8 ± 10%, p = 0.002). The risk of cardiovascular death was 26% lower in the ivabradine group, but in comparison with the control group statistical significance was not achieved [38].

Despite the fact that ETHIC-AHF was a small clinical trial, it was shown that intensification of treatment is particularly important during the period of highest sensitivity after hospitalization — during the first 30 days, while simultaneous administration of beta-adrenolytic and ivabradine to patients stabilized after decompensation, results in a significant decrease in HR and improvement of the LVEF, both in short and long term observation [38].

Summary

The profile of a patient with HR has changed significantly in recent years. Today's patients have do not only have different clinical characteristics, but also different needs than those treated a few years ago. Currently, there is a need for drugs that not only reduce the risk of death in patients with heart failure, but also have beneficial effects on the risk of repeated hospitalizations, normalizing hemodynamic parameters and improving the tolerance of exercise. Ivabradine turned out to be such a drug, which not only significantly reduces HR but also positively affects all the above-mentioned parameters, at the same time being the most modern form of treatment in patients with heart failure. Only further optimization of pharmacotherapy — especially with drugs with a well-proven beneficial effect on patient prognosis — can contribute to the improvement of long-term survival in this group.

Conflict(s) of interest

The Expert Group aims to ensure independence and objectivity in all its educational activities.

The aim of the activities of the Group of Experts which led to the present study are not intended to promote, support or specifically recommend a commercial product that is described in the article. Authors do not declare any conflict of interest.

Streszczenie

Przyspieszona częstość rytmu serca stanowi czynnik ryzyka śmiertelności ogólnej oraz sercowo-naczyniowej w różnych populacjach pacjentów. Stosowanie klasycznych leków zwalniających rytm serca, takich jak beta-adrenolityki czy antagoniści wapnia z grupy niedihydropirydynowych (werapamil i diltiazem), jest często ograniczone z powodu ich działań niepożądanych. Iwabradyna jest unikatowym, nowoczesnym lekiem, którego mechanizm działania polega na blokowaniu prądu I_f w węźle zatokowo-przedsionkowym. Przekłada się to na zmniejszenie częstości rytmu serca — parametru związanego z niekorzystnym rokowaniem u pacjentów z niewydolnością serca (HF). Niniejszy dokument stanowi opinię grupy ekspertów będącą podsumowaniem aktualnej wiedzy dotyczącej iwabradyny i jej zastosowania w populacji chorych z HF.

Słowa kluczowe: optymalizacja terapii, niewydolność serca, iwabradyna

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