EPIT-HF survey chronického srdcového zlyhávania s redukovanou, mid-range a zachovanou ejekčnou frakciou na Slovensku. 2. časť: Terapia

Dúbrava J, Šidlo R

[1]*Oddelenie neinvazívnej kardiológie, Nemocnica sv. Cyrila a Metoda, Univerzitná nemocnica Bratislava, Slovenská republika*

Dúbrava J, Šidlo R. EPIT-HF survey chronického srdcového zlyhávania s redukovanou, mid-range a zachovanou ejekčnou frakciou na Slovensku. 2. časť: Terapia. Cardiology Lett. 2018;27(1):5–19

Abstrakt. *Pozadie:* Existuje len minimum údajov o liečbe chronického srdcového zlyhávania (SZ) v reálnej praxi na Slovensku. O terapii SZ s „mid-range" ejekčnou frakciou (HFmrEF) neboli u nás doposiaľ publikované žiadne údaje.

Ciele: V prospektívnom prieskume stanoviť a vzájomne porovnať farmakologickú a nefarmakologickú liečbu troch fenotypov chronického SZ (SZ s redukovanou ejekčnou frakciou – HFrEF, SZ so zachovanou ejekčnou frakciou – HFpEF a HFmrEF). Stanoviť preskripčné preferencie liekov v rámci jednotlivých liekových skupín.

Metodika: Prieskum realizovalo 161 lekárov, z toho 115 kardiológov (71,4 %) a 46 internistov (28,6 %). Zaraďovali sa následní ambulantní pacienti s diagnózou chronického SZ starší ako 18 rokov. V prieskume neexistovali žiadne exklúzne kritériá. Fenotypy SZ boli definované podľa ejekčnej frakcie ĽK (EFĽK): HFrEF – EFĽK < 40 %, HFmrEF – EFĽK 40 – 49 %, HFpEF – EFĽK ≥ 50 %. Do prieskumu EPIT-HF bolo zaradených 2 677 pacientov. Podsúbory HFrEF, HFmrEF a HFpEF tvorilo 1 169 (43,7 %), 720 (26,9 %), respektíve 788 (29,4 %) pacientov.

Z [1]Oddelenia neinvazívnej kardiológie, Nemocnica sv. Cyrila a Metoda, Univerzitná nemocnica Bratislava a [2]Fakulty hospodárskej informatiky, Ekonomická univerzita, Bratislava, Slovenská republika

Do redakcie došlo dňa 17. októbra 2017; prijaté dňa 30. októbra 2017

Adresa pre korešpondenciu: MUDr. Juraj Dúbrava, PhD., Oddelenie neinvazívnej kardiológie, Nemocnica sv. Cyrila a Metoda, UNB, Antolská 11, 851 07 Bratislava, Slovenská republika, e-mail: dubrava@pe.unb.sk

EPIT-HF survey of chronic heart failure with reduced, mid-range and preserved ejection fraction in Slovakia. Part 2: Focus on therapy

Dubrava J, Sidlo R

[1]*Department of non-invasive cardiology, Sts. Cyril and Method Hospital, University Hospital Bratislava, Slovak Republic*

Dubrava J, Sidlo R. **EPIT-HF survey of chronic heart failure with reduced, mid-range and preserved ejection fraction in Slovakia**. **Part 2: Focus on therapy.** Cardiology Lett. 2018;27(1):5–19

Abstract. *Background:* There is only minimal data on the treatment of chronic HF in real practice in Slovakia. For the therapy of heart failure with mid-range ejection fraction (HFmrEF), no Slovak data has yet been published.

Aims: In a prospective survey, to determine and compare the pharmacological and non-pharmacological treatment for three phenotypes of chronic heart failure (HF) – HF with reduced ejection fraction (HFrEF), HFmrEF and HF with preserved ejection fraction (HFpEF). We also investigated drug prescription preferences within individual drug classes.

Methods: The survey was carried out by 161 physicians (115 cardiologists – 71.4% and 46 internists – 28.6%). Consecutive outpatients diagnosed with chronic HF aged at least 18 years were enrolled. There were no exclusion criteria in the survey. The HF phenotypes were defined according to the left ventricular ejection fraction (LVEF): HFrEF – LVEF < 40%, HFmrEF – LVEF 40-49%, HFpEF – LVEF ≥ 50%. A total of 2 677 patients were enrolled in the EPIT-HF survey. The subgroups of HFrEF, HFmrEF

From [1]Department of non-invasive cardiology, Sts. Cyril and Method Hospital, University Hospital Bratislava and [2]Faculty of economic informatics, Slovak Republic

Manuscript received October 17, 2017; accepted for publication October 30, 2017

Address for correspondence: Juraj Dúbrava, M.D., PhD., Department of non-invasive cardiology, Sts. Cyril and Method Hospital, University Hospital Bratislava, Antolská 11, 851 07 Bratislava, Slovak Republic, e-mail: dubrava@pe.unb.sk

Výsledky: Pri porovnaní liečby troch typov SZ sme zistili najvýraznejší rozdiel medzi HFrEF a HFpEF. Medzi týmito fenotypmi bol významný rozdiel v prevalencii liečby všetkými liekovými skupinami, CRT-D, CRT-P a ICD. Farmakoterapia HFmrEF sa viac približovala liečbe HFrEF ako liečbe HFpEF. Prevalencia terapie HFmrEF ľubovoľnou liekovou skupinou, respektíve CRT-D, CRT-P a ICD, bola vždy intermediárna medzi prevalenciou pri HFrEF a HFpEF. Preferencie jednotlivých liekov v rámci betablokátorov, inhibítorov enzýmu konvertujúceho angiotenzín a antagonistov AT_1 receptora pre angiotenzín II sú na Slovensku odlišné od európskeho registra ESC HF-LT. V prieskume EPIT-HF boli najčastejšie indikovanými liekmi v uvedených liekových skupinách pri všetkých fenotypoch SZ bisoprolol, perindopril a telmisartan.

Záver: V prospektívnom prieskume EPIT-HF sme prezentovali „real-world" údaje o farmakologickej a nefarmakologickej liečbe všetkých troch fenotypov SZ na Slovensku. Údaje o liečbe HFmrEF sú prioritné. Obr. 4, Tab. 4, Lit. 28, online full text (Free, PDF), www.cardiologyletters.sk

Kľúčové slová: chronické srdcové zlyhávanie – srdcové zlyhávanie s redukovanou ejekčnou frakciou – srdcové zlyhávanie s mid-range ejekčnou frakciou – srdcové zlyhávanie so zachovanou ejekčnou frakciou – liečba

Results: When comparing the treatment for three types of HF, we found the most striking differences between HFrEF and HFpEF. Among these phenotypes, there were significant differences in the treatment prevalence across all drug classes, CRT-D, CRT-P and ICD. Pharmacotherapy for HFmrEF has been more closely related to HFrEF treatment than to HFpEF treatment. The prevalence of therapy for HFmrEF by any drug class, CRT-D, CRT-P and ICD, was always intermediate between the prevalence of therapy for HFrEF and HFpEF. Drug preferences for beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers were different in Slovakia from those in the ESC HF Long-Term registry. In the EPIT-HF survey, the most commonly used drugs in these drug classes were bisoprolol, perindopril and telmisartan for all phenotypes of HF.

Conclusion: In the prospective EPIT-HF survey, we presented real-world data on the pharmacological and non-pharmacological treatment of all three phenotypes of HF in Slovakia. Data on HFmrEF treatment are a priority. Fig. 4, Tab. 4, Ref. 28, online full text (Free, PDF), www.cardiologyletters.sk

Key words: chronic heart failure – heart failure with reduced ejection fraction – heart failure with mid-range ejection fraction – heart failure with preserved ejection fraction – therapy

Podľa odporúčaní Európskej kardiologickej spoločnosti (ESC) sa od roku 2016 rozlišujú tri fenotypy chronického srdcového zlyhávania (SZ) podľa hodnoty ejekčnej frakcie ľavej komory (EFĽK): SZ s redukovanou ejekčnou frakciou (HFrEF, heart failure with reduced ejection fraction), SZ s mid-range ejekčnou frakciou (HFmrEF, heart failure with mid-range ejection fraction) a SZ so zachovanou ejekčnou frakciou (HFrEF, heart failure with preserved ejection fraction) (1).

Evidence-based medicine pri jednotlivých typoch SZ sa diametrálne odlišuje. U pacientov s HFrEF existuje podľa výsledkov obrovských klinických štúdií nespochybniteľná medicína dôkazov pre viaceré liekové skupiny v zmysle redukcie mortality a morbidity. Na rozdiel od toho pri HFpEF žiadna lieková skupina nepreukázala morbi-mortalitný benefit a terapia je zameraná na komorbidity. Doposiaľ nebola publikovaná žiadna prospektívna štúdia špecificky fokusovaná na liečbu HFmrEF. Pri tomto type SZ sú poznatky o liečbe najslabšie.

Podľa registrov ESC-HF Pilot a ESC-HF-LT existujú značné regionálne rozdiely v liečbe chronického SZ v Európe (2, 3). Podľa prieskumu IMPACT RECO existuje aj vo vyspelých krajinách u týchto pacientov významný rozdiel medzi odporúčaniami a klinickou praxou (4). Väčšina registrov pri chronickom SZ sa týkala hospitalizovaných pacientov (5). Existuje len minimum údajov o liečbe chronického SZ v reálnej praxi na Slovensku (6), pričom o terapii HFmrEF neboli doposiaľ u nás publikované žiadne údaje. Tieto sku-

According to the guidelines of the European Society of Cardiology (ESC), three phenotypes of chronic heart failure (HF) have been distinguished since the the year 2016, depending on the left ventricular ejection fraction (LVEF): HF with reduced ejection fraction (HFrEF), heart failure with mid-range ejection fraction (HFmrEF) and heart failure with preserved ejection fraction (HFpEF) (1).

Evidence-based medicine for each type of chronic HF is diametrically different. In patients with HFrEF, there is strong evidence for several drug classes in terms of mortality and morbidity reduction, according to the results of robust clinical trials.

In contrast, in HFpEF, no drug class has shown convincing morbidity-mortality benefit and therapy is focused on comorbidities. No prospective study, specifically focused on HFmrEF, has been published so far. In this type of HF, knowledge about the treatment is the most limited.

According to ESC-HF Pilot and ESC HF Long-Term registries, there are significant regional differences in the treatment of chronic HF in Europe (2, 3). The IMPACT RECO survey has also shown a significant gap between the guidelines and clinical practice in these patients in developed countries (4).

Most registries in chronic HF concerned hospitalized patients (5). There exist only minimal data on the treatment of chronic HF in real-life practice in Slovakia (6), and no data have been published yet about HFmrEF therapy.

točnosti nás viedli k projektu EPIT-HF (**Epi**demiology and **T**herapy for **H**eart **F**ailure), ktorý bol zameraný na klinické charakteristiky a liečbu jednotlivých fenotypov chronického SZ u ambulantných pacientov. V práci prezentujeme prvé slovenské „real-world" údaje o farmakologickej a nefarmakologickej liečbe všetkých troch fenotypov SZ.

Pacienti a metodika

EPIT-HF je prospektívna neintervenčná observačná multicentrická štúdia. Prieskum realizovalo 161 lekárov, z toho 115 kardiológov (71,4 %) a 46 internistov (28,6 %). Každý lekár mal prospektívne zaradiť 20 následných ambulantných pacientov s diagnózou chronického SZ, stanovenou podľa odporúčaní ESC, platných v čase realizácie štúdie (7). Podmienkou pre zaradenie bol vek ≥ 18 rokov. Neexistovali žiadne exklúzne kritériá pre zaradenie pacientov. Pacienti mohli byť zaradení bez ohľadu na doterajšiu liečbu. Echokardiografické údaje sa týkali posledného dostupného vyšetrenia pred zaradením do prieskumu, vrátane dňa zaradenia. Prieskum sa vykonával dotazníkovou formou. Údaje sa získavali počas jediného vyšetrenia. Nábor sa realizoval v októbri a novembri 2015. Prieskum nebol zameraný na nijaký konkrétny liek.

Participujúci lekári zaradili do prieskumu spolu 3 280 pacientov. Z tohto počtu boli echokardiografické údaje dostupné u 2 677 pacientov (81,6 %). Títo pacienti predstavovali súbor prezentovanej práce. V prieskume sme porovnali prevalenciu jednotlivých modalít farmakologickej a nefarmakologickej liečby medzi tromi fenotypmi SZ (HFrEF, HFmrEF, HFpEF), definovanými podľa aktuálnych odporúčaní ESC podľa hodnoty EFĽK: HFrEF – EFĽK < 40 %, HFmrEF – EFĽK 40 – 49 %, HFpEF – EFĽK ≥ 50 % (1). Lekári registrovali údaje o liečbe chronického SZ, ktorú pacienti užívali najmenej počas 7 dní pred vstupom do prieskumu. Konkrétne sme hodnotili nasledovné liekové skupiny, respektíve modality, ktoré sa používali na Slovensku roku 2015: 1. Farmakoterapia: betablokátory (BB), inhibítory angiotenzín konvertujúceho enzýmu (ACEI), antagonisty AT_1 receptora pre angiotenzín II (ARB), antagonisty mineralokortikoidných receptorov (MRA), ivabradín, tiazidy, furosemid a digoxín. 2. Nefarmakologická liečba: implantovateľný defibrilátor s možnosťou resynchronizačnej liečby (CRT-D), implantovateľný kardiostimulátor s možnosťou resynchronizačnej liečby (CTP-P), implantovateľný kardioverter-defibrilátor (ICD), transplantácia srdca (HTx), podporné komorové systémy.

Štatistická analýza

Kategorické údaje sú vyjadrené relatívnymi početnosťami. Spojité premenné vyjadrujeme ako priemer ± smerodajná odchýlka. Frekvenciu výskytu kategorických údajov medzi

These facts were the main reason for the EPIT-HF (**Epi**demiology and **T**herapy for **H**eart **F**ailure) survey, which focused on the clinical characteristics and treatment of individual phenotypes of chronic HF in outpatients. We present the first Slovak real-world data on the pharmacological and non-pharmacological treatment of all three phenotypes of HF.

Patients and methods

EPIT-HF is a prospective non-interventional observational multicenter study. The survey was carried out by 161 physicians, including 115 cardiologists (71.4%) and 46 internists (28.6%). Each physician had to include prospectively 20 outpatients diagnosed with chronic HF according to the ESC guidelines valid at the time of the study realization (7). Patients had to be aged at least 18 years. They could be included regardless of previous treatment. There were no exclusion criteria. Echocardiographic data were obtained from the last available examination prior to the survey, including the date of enrollment. The survey was conducted using a questionnaire form. The data were obtained during a single examination. Recruitment took place in October and November 2015. The survey was not focused on a specific drug. Participating physicians included a total of 3 280 patients. Out of this group, echocardiographic data were available in 2 677 patients (81.6%). These patients represented a study group of the presented survey. In the survey, we compared the prevalence of the pharmacological and non-pharmacological treatment modalities between the three HF phenotypes (HFrEF, HFmrEF, HFpEF), defined according the current ESC guidelines: HFrEF – LVEF < 40%, HFmrEF – LVEF 40-49%, HFpEF – LVEF ≥ 50% (1). Data on the treatment of chronic HF that the patients have been using for the last 7 days prior to entering the study were obtained. In particular, we evaluated the following drug classes and other modalities that were used in Slovakia in 2015: 1. pharmacotherapy: beta-blockers (BB), angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), mineralocorticoid receptor antagonists (MRA), ivabradine, thiazides, furosemide and digoxin, 2. non-pharmacological treatment: cardiac resynchronization therapy defibrillator (CRT-D), cardiac resynchronization therapy pacemaker (CRT-P), implanted cardioverter-defibrillator (ICD), heart transplantation (HTx) and ventricular assist devices.

Statistical analysis

Categorial values are expressed as percentages. Continuous variables are given as mean ± standard deviation. The occurrence of categorial data between the subsets was

podsúbormi sme porovnali Pearsonovým χ^2 testom nezávislosti, respektíve Fisherovým presným testom. Na porovnanie stredných hodnôt spojitých premenných medzi podsúbormi sme použili analýzu rozptylu (ANOVA). V prípade, že výsledok ANOVA bol štatisticky významný, ďalej sme použitím metódy LSD skúmali, medzi ktorými podsúbormi bol výsledok štatisticky významný. Ako hranicu štatistickej významnosti sme zvolili hodnotu $p < 0,05$. Všetky kalkulácie sa realizovali pomocou SPSS Statistics 20.0 software (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.).

compared by the Pearson´s χ^2 test of independence or Fisher´s exact test. The differences between mean values of continuous variables were compared using analysis of variance (ANOVA). If the ANOVA result was statistically significant, we subsequently determined statistical significance of differences between the subsets using the LSD method. As a limit of statistical significance, we have chosen $p < 0.05$. All calculations were made using SPSS Statistics 20.0 software (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0, Armonk, NY: IBM Corp.).

Výsledky

Podsúbory pacientov s HFrEF, HFmrEF a HFpEF zahŕňali 1 169 (43,7 %), 720 (26,9 %), respektíve 788 (29,4 %) pacientov. Základné klinické charakteristiky sú uvedené v **tabuľke 1**. Zistili sme významné rozdiely pre porovnanie

Results

Subgroups of patients with HFrEF, HFmrEF and HFpEF included 1 169 (43.7%), 720 (26.9%) and 788 (29.4%) patients, respectively. The basic clinical characteristics are shown in **Table 1**. We have identified significant differ-

Table 1 Clinical characteristics
Tabuľka 1 *Klinické charakteristiky*

	Heart failure *(Srdcové zlyhávanie)*			**P**			
	HFrEF (n=1 169)	HFmrEF (n=720)	HFpEF (n=788)	Overall	1 vs 2	1 vs 3	2 vs 3
Demography *(Demografia)*							
Age (years)	66.2±10.9	68.2±10.2	69.2±9.5	**<0.001**	**<0.001**	**<0.001**	0.066
Female gender	31.3%	40.1%	49.9%	**<0.001**	**<0.001**	**<0.001**	**<0.001**
NYHA class I+II	48.3%	61.8%	72.8%	**<0.001**	**<0.001**	**<0.001**	**<0.001**
NYHA class ≥ III	51.7%	38.2%	27.2%	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Clinical signs *(Klinické znaky)*							
BMI (kg/m^2)	28.7±5.0	29.7±4.9	29.8±4.9	**<0.001**	**<0.001**	**<0.001**	0.835
SBP (mmHg)	128.2±17.8	135.1±17.4	133.7±16.6	<0.001	<0.001	<0.001	0.108
DBP (mmHg)	77.5±10.4	79.9±10.4	79.0±10.1	**<0.001**	**<0.001**	**0.002**	0.074
Heart rate (bpm)	73.5±13.0	74.5±14.9	71.7±12.6	**<0.001**	0.115	**0.003**	**<0.001**
Primary cause of heart failure *(Primárna príčina srdcového zlyhávania)*							
CAD	60.4%	64.3%	35.8%	**<0.001**	0.097	**<0.001**	**<0.001**
Hypertension	6.9%	15.6%	39.0%	**<0.001**	**<0.001**	**<0.001**	**<0.001**
D-CMP	25.9%	8.2%	3.1%	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Valvular disease	5.7%	10.0%	15.9%	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Other causes	0.9%	1.8%	6.4%	**<0.001**	0.137	**<0.001**	**<0.001**
Selected comorbidities *(Vybrané komorbidity)*							
Myoc. infarction	54.1%	50.6%	29.1%	**<0.001**	0.142	**<0.001**	**<0.001**
Hypertension	85.0%	92.6%	93.7%	<0.001	<0.001	<0.001	0.475
Diabetes mellitus	42.5%	49.3%	43.9%	**0.005**	**0.004**	0.542	**0.036**
AFib/AFlu	38.2%	41.3%	38.8%	0.396	0.191	0.776	0.344
Stroke*	14.8%	14.6%	13.7%	0.475	0.898	0.499	0.625
Malignancy**	5.7%	10.6%	8.0%	**0.001**	**<0.001**	**0.049**	0.086

HFrEF – heart failure with reduced ejection fraction *(srdcové zlyhávanie s redukovanou ejekčnou frakciou; 1),* HFmrEF – heart failure with mid-range ejection fraction *(srdcové zlyhávanie s mid-range ejekčnou frakciou; 2)*, HFpEF – heart failure with preserved ejection fraction *(srdcové zlyhávanie so zachovanou ejekčnou frakciou; 3),* overall *(celkovo),* age (years) – *vek (roky),* female gender *(ženské pohlavie),* class *(trieda), BMI* – body mass index, SBP – systolic blood pressure *(systolický tlak krvi)*, DBP – diastolic blood pressure *(diastolický tlak krvi)*, heart rate *(srdcová frekvencia),* CAD – coronary artery disease *(koronárna artériová choroba)*, hypertension *(hypertenzia)*, D-CMP – dilated cardiomyopathy *(dilatačná kardiomyopatia)*, valvular diseases *(chlopňové chyby),* other causes (*iné príčiny)*, myoc. infarction *(infarkt myokardu),* AFib – atrial fibrillation *(fibrilácia predsení)*, AFlu – atrial flutter *(flutter predsení)*, stroke *(mozgová príhoda),* * – ischemic stroke *(ischemická mozgová príhoda)* + intraparenchymal hemorrhage *(parenchýmová hemorágia)* + subarachnoidal hemorrhage *(subarachnoidálna hemorágia)*, malignancy *(malignita),* **– active malignancy *(aktívna malignita)* + malignancy in remission *(malignita v remisii)*. Continuous variables are expressed as mean ± standard deviation *(spojité premenné sú vyjadrené ako priemer ± smerodajná odchýlka)*.

takmer všetkých charakteristík medzi jednotlivými fenotypmi SZ (demografické faktory, klinické znaky, primárna príčina SZ a komorbidity), s výnimkou prevalencie cievnych mozgových príhod a fibrilácie/flutteru predsiení.

V **tabuľke 2** je porovnanie liečby pri troch typoch chronického SZ. Zistili sme, že preskripcia farmakoterapie a elektroimpulzoterapie v praxi sa medzi nimi významne odlišuje. Najmarkantnejšie diferencie v liečbe sme zistili medzi HFrEF a HFpEF – pri všetkých modalitách farmakoterapie a elektroimpulznej terapie sme zistili vysoko signifikantný prevalenčný rozdiel. Pri všetkých položkách bol významne vyšší podiel liečby v prospech HFrEF okrem ARB a tiazidov, ktoré sa významne častejšie používali pri HFpEF.

Pri porovnaní HFmrEF a HFpEF sme zistili významne odlišnú preskripciu všetkých terapeutických modalít okrem digoxínu a CRT. Významne vyššia preskripcia liečby bola pri HFmrEF s výnimkou ARB a tiazidov, ktoré sa významne častejšie indikovali pri HFpEF.

Pri komparácii HFrEF a HFmrEF bol významne rozdielny podiel terapie jednotlivými liekovými skupinami (okrem BB a kombinácie BB + ACEI/ARB) a elektroimpulzoterapie. Vo všetkých položkách bola významne vyššia prevalencia liečby v prospech HFrEF, opäť s výnimkou ARB a tiazidov.

Na **obrázku 1** je voľba jednotlivých BB pri chronickom SZ. Absolútne najčastejšie sa pri všetkých troch fenotypoch SZ používa bisoprolol. Vysoký a vzájomne porovnateľný je

ences for comparison of almost all characteristics between three HF phenotypes (demography, clinical signs, primary cause of HF and comorbidities) except for the prevalence of stroke and atrial fibrillation/atrial flutter.

The comparison of treatment in all phenotypes of chronic HF is given in **Table 2**. We have found that the use of pharmacotherapy and electroimpulse therapy (CRT-D, CRT-D and ICD) was significantly different between HF types. The most remarkable differences were found between HFrEF and HFpEF – significant difference of prevalence was identified for all drug classes and all modalities of electroimpulse therapy. For these items, there was a significantly higher proportion of treatment in HFrEF except for ARBs and thiazides, which were more commonly used in HFpEF.

When comparing HFmrEF and HFpEF, we found a significantly different prescription of all therapeutic modalities except for digoxin and CRT. There was significantly higher prescription in HFmrEF with the exception of ARB and thiazides, which were more frequently indicated in HFpEF.

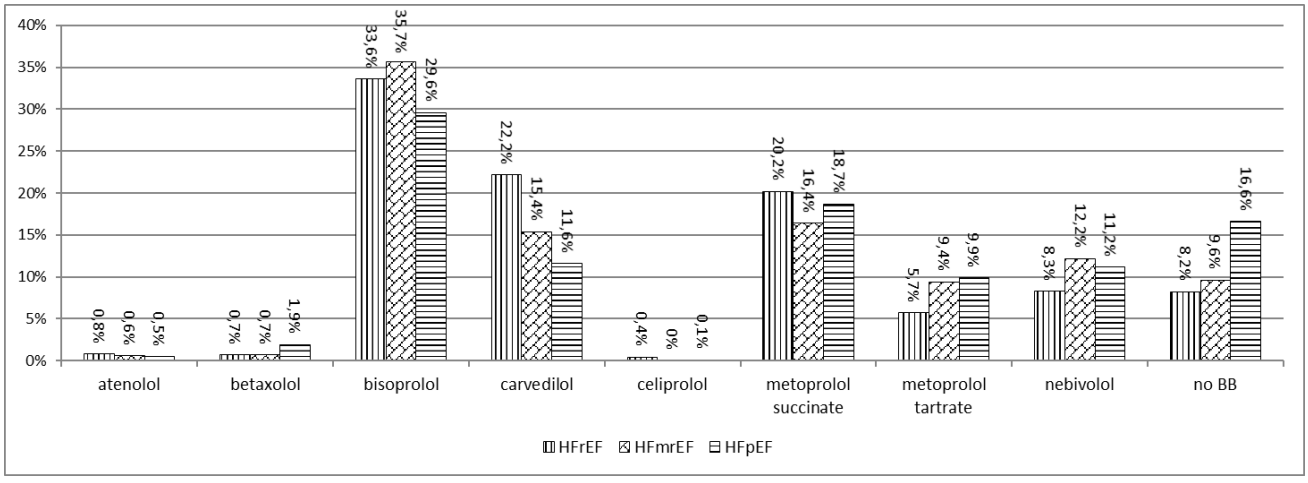
Comparison of HFrEF and HFmrEF has shown significantly different rate of treatment with individual drug classes (except for BB and the combination BB + ACEI/ARB) and electroimpulse therapy. In all items there was a significantly higher prevalence of treatment in favour of HFrEF, again with the exception of ARB and thiazides.

Figure 1 shows the choice of BB in chronic HF. Bisoprolol was absolutely the most frequent choice in all three

Table 2 Comparison of treatment for individual types of chronic heart failure
Tabuľka 2 *Porovnanie liečby jednotlivých typov chronického srdcového zlyhávania*

	Heart failure *(Srdcové zlyhávanie)*			**P**			
	HFrEF (n=1 169)	HFmrEF (n=720)	HFpEF (n=788)	Overall	1 vs 2	1 vs 3	2 vs 3
Beta-blockers	91.9%	90.4%	83.4%	**<0.001**	0.275	**<0.001**	**<0.001**
ACEI	77.4%	71.1%	62.9%	**<0.001**	**0.003**	**<0.001**	**<0.001**
ARB	18.7%	23.3%	29.1%	**<0.001**	**0.016**	**<0.001**	**0.012**
ACEI/ARB	92.8%	92.9%	87.7%	**<0.001**	1.0	**<0.001**	**<0.001**
MRA	80.1%	55.4%	28.9%	**<0.001**	**<0.001**	**<0.001**	**<0.001**
BB+ACEI/ARB	85.7%	84.7%	73.9%	**<0.001**	0.592	**<0.001**	**<0.001**
BB+ACEI/ARB+MRA	69.3%	49.3%	21.6%	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Ivabradine	39.7%	34.7%	28.1%	**<0.001**	**0.032**	**<0.001**	**0.005**
Ivabradine+BB	35.6%	30.8%	21.6%	**<0.001**	**0.036**	**<0.001**	**<0.001**
Thiazides	11.7%	16.5%	29.4%	**<0.001**	**0.004**	**<0.001**	**<0.001**
Furosemide	89.9%	75.0%	54.7%	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Digoxin	24.8%	15.8%	12.7%	**<0.001**	**<0.001**	**<0.001**	0.089
CRT-D	8.2%	0.8%	0.4%	**<0.001**	**<0.001**	**<0.001**	0.324
CRT-P	2.7%	1.0%	0.5%	**<0.001**	**0.008**	**<0.001**	0.369
ICD	16.2%	2.2%	0.8%	**<0.001**	**<0.001**	**<0.001**	0.029
HTx	0.3%	0%	0.6%	0.104	0.304	0.498	0.063
Assist devices	0.3%	0%	0.1%	0.367	0.292	0.653	1.0

Legend as in Table 1 *(legenda ako v tabuľke 1)*. BB – beta-blockers *(betablokátory)*, ACEI – angiotensin-converting enzyme inhibitors *(inhibítory angiotenzín konvertujúceho enzýmu)*, ARB – angiotensin II receptor blockers *(antagonisty receptora pre angiotenzín II)*, MRA – mineralocorticoid receptor antagonists *(antagonisty mineralokortikoidových receptorov)*, thiazides *(tiazidy)*, CRT-D – cardiac resynchronization therapy defibrillator *(implantovateľný defibrilátor s možnosťou resynchronizačnej liečby)*, CRT-P – cardiac resynchronization therapy pacemaker *(implantovateľný kardiostimulátor s možnosťou resynchronizačnej liečby)*, ICD – implanted cardioverter-defibrillator *(implantovateľný kardioverter-defibrilátor)*, HTx – heart transplantation *(transplantácia srdca)*, assist devices *(podporné systémy)*



	1 vs 2	1 vs 3	2 vs 3
atenolol	0.777	0.579	1.0
betaxolol	1.0	**0.018**	**0.044**
bisoprolol	0.370	0.061	**0.011**
carvedilol	**<0.001**	**<0.001**	**0.028**
celiprolol	0.164	0.411	1.0
metoprolol succinate	**0.045**	0.416	0.251
metoprolol tartrate	**0.002**	**<0.001**	0.794
nebivolol	**0.007**	**0.04**	0.574
no beta-blocker	0.315	**<0.001**	**<0.001**

Figure 1 Beta-blockers (BB) therapy for individual types of chronic heart failure
Obrázok 1 *Liečba betablokátormi (BB) pri jednotlivých typoch chronického srdcového zlyhávania*
HFrEF – heart failure with reduced ejection fraction (1) *(srdcové zlyhávanie s redukovanou ejekčnou frakciou (1),* HFmrEF – heart failure with mid-range ejection fraction (2) *(srdcové zlyhávanie s „mid-range" ejekčnou frakciou (2),* HFpEF – heart failure with preserved ejection fraction (3) *(srdcové zlyhávanie so zachovanou ejekčnou frakciou (3),* NS – nonsignificant difference *(nevýznamný rozdiel),* no *(žiadny).* Percentages represent the proportion of patients treated with the given drug *(Percentá vyjadrujú podiel pacientov liečených daným liekom).*

aj podiel pacientov, ktorí sú liečení karvedilolom a metoprololom sukcinátom. V menšej miere sa používajú nebivolol a metoprolol tartarát. Použitie ostatných BB je zanedbateľné.

Prehľad preskripcie ACEI je na **obrázku 2**. Pri všetkých typoch SZ má úplne dominantné postavenie perindopril, bez signifikantného rozdielu medzi jednotlivými typmi. Často sa indikuje aj ramipril a trandolapril, pričom ich preskripcia pri všetkých typoch SZ je porovnateľná. Preskripcia ďalších šiestich ACEI je zanedbateľná.

Na **obrázku 3** je preskripcia ARB. Jej podiel je výrazne nižší ako pri ACEI. Pri všetkých troch typoch SZ sa uniformne najčastejšie používa telmisartan. Jeho preskripcia je významne častejšia pri HFpEF v porovnaní s HFrEF, respektíve HFmrEF.

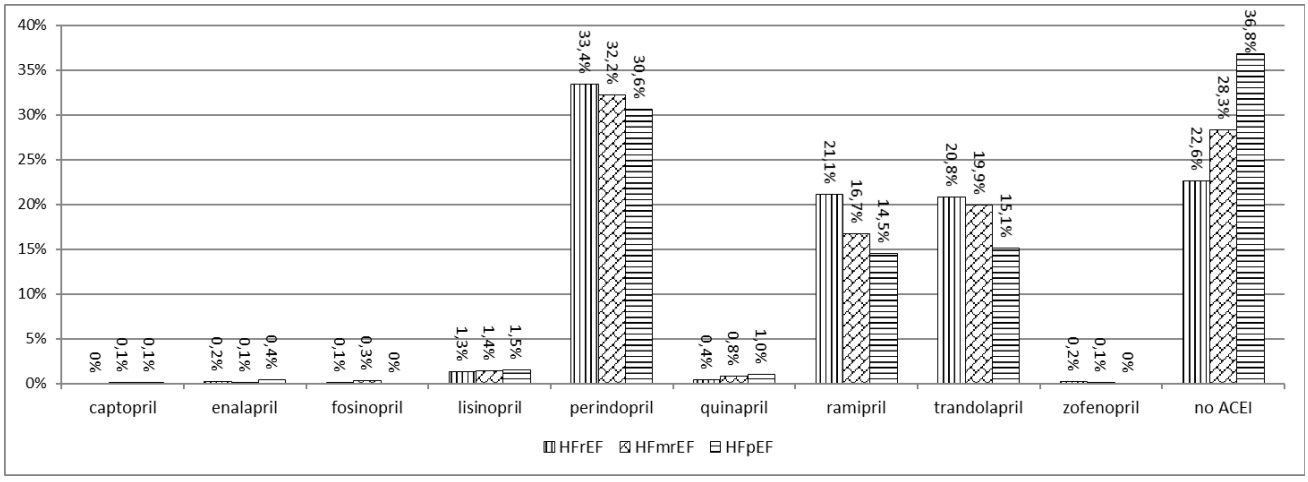
Obrázok 4 demonštruje podiel pacientov, liečených MRA. U pacientov s HFrEF sa najčastejšie používa eplerenón, kým pri HFmrEF a HFpEF je to spironolaktón. Obidva MRA sa signifikantne zriedkavejšie predpisujú pri HFpEF, ako pri HFrEF, respektíve HFmrEF.

phenotypes. The proportion of patients treated with carvedilol and metoprolol succinate was also high and comparable. To a lesser extent, nebivolol and metoprolol tartrate were used. The prescription of other BB was negligible.

An overview of ACEI prescription is shown in **Figure 2**. In all types of HF, perindopril was completely dominant, with no significant differences between the three phenotypes. Ramipril and trandolapril are also often indicated, and their prescription in all types of HF is comparable. Prescription of six other ACEIs is negligible.

Figure 3 shows ARB precription. The use of ARB was significantly lower than that of ACEI. In all three types of HF, telmisartan was most frequently used. Its precription was significantly more frequent in HFpEF compared to HFrEF and HFmrEF.

Figure 4 demonstrates the proportion of patients treated with MRA. In patients with HFrEF, eplerenone was most commonly used, whereas for HFmrEF and HFpEF it was



	1 vs 2	1 vs 3	2 vs 3
captopril	0.381	0.403	1.0
enalapril	1.0	0.4	0.626
fosinopril	0.562	1.0	0.228
lisinopril	0.839	0.695	1.0
perindopril	0.615	0.2	0.505
quinapril	0.351	0.156	0.793
ramipril	**0.02**	**<0.001**	0.255
trandolapril	0.639	**0.002**	**0.017**
zofenopril	1.0	0.519	0.478
no ACEI	**0.005**	**<0.001**	**<0.001**

Figure 2 Angiotensin-converting enzyme inhibitors (ACEI) therapy for individual types of chronic heart failure
Obrázok 2 *Liečba inhibítormi enzýmu konvertujúceho angiotenzín (ACEI) pri jednotlivých typoch srdcového zlyhávania*
Legend as in Figure 1 *(Legenda ako k obrázku 1)*

Analýza

Prieskum EPIT-HF umožňuje vzhľadom na kritérium zaraďovania za sebou nasledujúcich pacientov odhadnúť podiel jednotlivých fenotypov SZ v ambulantnej praxi. Dominuje HFrEF (menej ako 50 % všetkých pacientov). Podiel pacientov s HFmrEF a HFpEF je takmer rovnaký (do 30 %).

EPIT-HF je prvý prieskum na Slovensku, ktorý poskytuje epidemiologické údaje o liečbe všetkých troch fenotypov SZ.

Liečba HFrEF

V **tabuľke 3** je porovnanie liečby BB, ACEI/ARB a MRA pri HFrEF na Slovensku oproti veľkým registrom, prieskumom a štúdiám, do ktorých bolo zaradených aspoň 1 000 pacientov. Prevalencia liečby hlavnými liekovými skupinami je u slovenských pacientov minimálne rovnako dobrá ako vo vyspelých krajinách v priebehu posledných 10 rokov: BB 92 % vs 78 – 97 %, ACEI/ARB 93 % vs 80 – 93 %, MRA 80 % vs 18 – 68 %, ACEI/ARB + BB 86 % vs 61 – 79 %.

spironolactone. Both drugs were significantly less frequently prescribed in HFpEF than in HFrEF and HfmrEF.

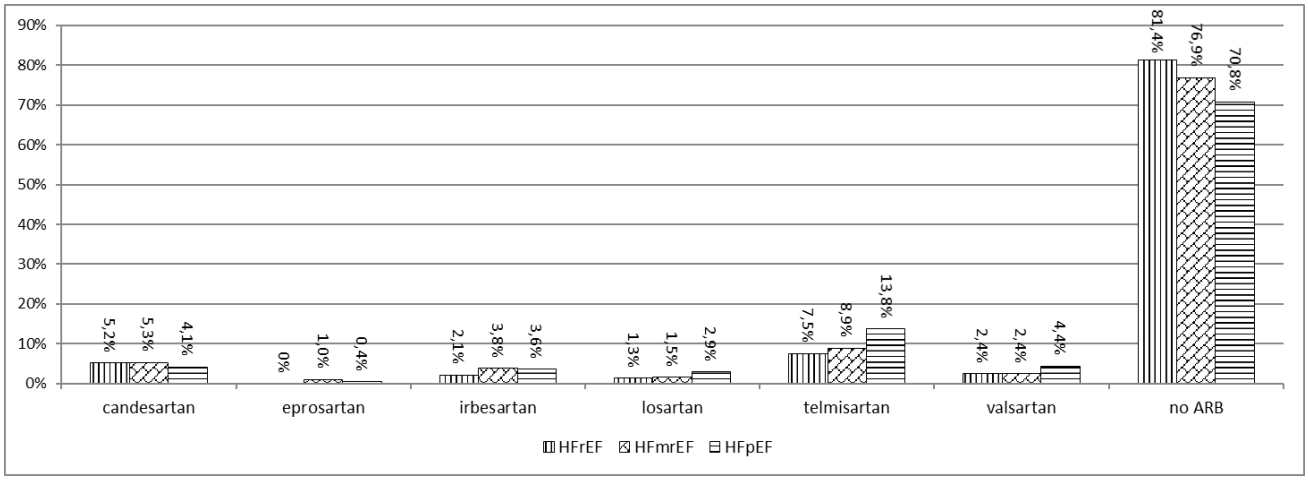
Analysis

The consecutive patients were included in the EPIT-HF survey. Therefore it was possible to estimate the proportion of HF phenotypes in outpatient practice. HFrEF dominated with less than 50% of all patients. The proportion of patients with HFmrEF and HFpEF was almost the same (up to 30%).

EPIT-HF is the first survey providing epidemiological data on the treatment of all three HF phenotypes in Slovakia.

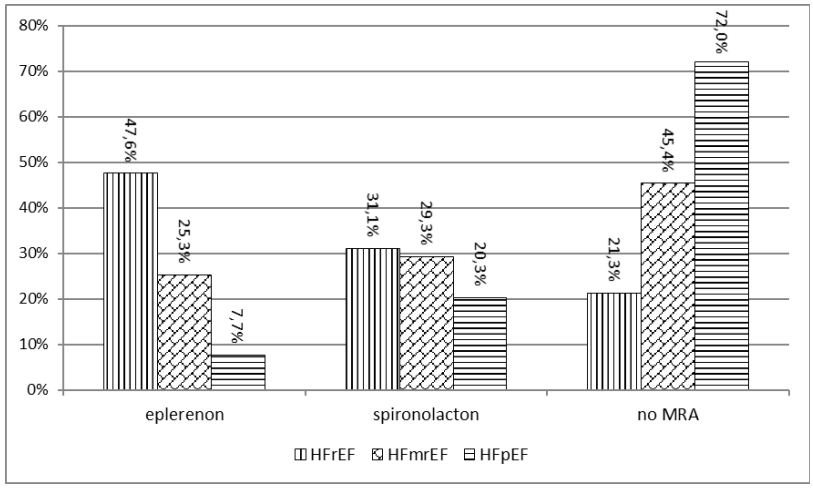
Therapy for HFrEF

Table 3 shows the comparison of treatment with BB, ACEI/ARB and MRA in HFrEF in Slovakia over the treatment in large registries, surveys and studies involving at least 1 000 patients. The prevalence of treatment with these major drug classes is



	1 vs 2	1 vs 3	2 vs 3
candesartan	1,0	0,279	0,273
eprosartan	**0,001**	0,065	0,208
irbesartan	**0,043**	0,065	0,891
losartan	0,687	**0,012**	0,082
telmisartan	0,297	**<0,001**	**0,003**
valsartan	1,0	**0,013**	**0,033**
no ARB	**0,022**	**<0,001**	**0,007**

Figure 3 Angiotensin receptor blockers (ARB) therapy for individual types of chronic heart failure
Obrázok 3 *Liečba antagonistami receptora pre angiotenzín II (ARB) pri jednotlivých typoch chronického srdcového zlyhávania*
Legend as in Figure 1 *(Legenda ako k obrázku 1)*



	1 vs 2	1 vs 3	2 vs 3
eplerenon	**<0.001**	**<0.001**	**<0.001**
spironolacton	0.411	**<0.001**	**<0.001**
no MRA	**<0.001**	**<0.001**	**<0.001**

Figure 4 Mineralocorticoid receptor antagonists (MRA) therapy for individual types of chronic heart failure
Obrázok 4 *Liečba antagonistami mineralokortikoidových receptorov (MRA) pri jednotlivých typoch chronického srdcového zlyhávania*
Legend as in Figure 1 *(Legenda ako k obrázku 1)*

Table 3 Prevalence of treatment with beta-blockers, ACEI/ARB and MRA in patients with HFrEF
Tabuľka 3 *Prevalencia liečby betablokátormi, ACEI/ARB a MRA u pacientov s HFrEF*

Authors *(Autori)*	n	Type *(Typ)*	BB	ACEI/ARB	MRA	ACEI/ARB + BB
Chin[28] (2016)	83 605	meta-analysis	81.4%	79.8%	36.4%	-
Fonarow[25] (2008)	15 381*	IMPROVE-HF trial	86%	80%	36%	-
Peterson[26] (2013)	12 556*	NCDR PINNACLE program	92%	85%	-	79%
Jankowska[14] (2014)	5 563	DATA-HELP registry	97%	94%	64%	-
Chioncel[27] (2017)	5 460	ESC HF-LT registry	92.9%	91.7%	67.8%	-
Crespo-Leiro[8] (2015)	2 625	ESC HF-LT subregistry	93.3%	92.6%	74.5%	-
Pascual-Figal[15] (2017)	2 351*	REDINSCOR I, MUSIC registries	81.1%	87.2%	58.4%	-
Zugck[12] (2014)	1 956	INTENSIFY trial	77.8%	83%	18%	-
de Groote[4] (2007)	1 919*	IMPACT RECO survey	65%	92%	35%	61%
von Scheidt[13] (2014)	1 853	EVITA-HF registry	86%	85%	47%	-
Dubrava (2018)	1 169*	EPIT-HF survey	91.9%	92.8%	80.1%	85.7%

HFrEF – heart failure with reduced ejection fraction *(srdcové zlyhávanie s redukovanou ejekčnou frakciou)*, ACEI – angiotensin-converting enzyme inhibitors *(inhibítory angiotenzín konvertujúceho enzýmu)*, ARB – angiotensin II receptor blockers *(antagonisty receptora pre angiotenzín II)*, BB – beta-blockers *(betablokátory)*, MRA – mineralocorticoid receptor antagonists *(antagonisty mineralokortikoidových receptorov)*, * – outpatients *(ambulantní pacienti)*

Vzhľadom na uvedené hodnoty nie sú odhadované rezervy („gaps“) v liečbe ACEI/ARB, respektíve BB veľké. Nezdôvodniteľné podliečenie („true undertreatment“) sa uvádza pre ACEI/ARB 3,2 – 13,1 %, pre BB 1,8 – 3,9 % (1, 8, 9). Vyššie rezervy sú pri podliečení MRA – 5,4 – 16,8 % (1, 8, 9). Nedostatočná adherencia k liečbe ACEI/ARB, BB a MRA zvyšuje u pacientov s HFrEF 2,2 – 2,3-násobne celkovú mortalitu, kardiovaskulárnu mortalitu a mortalitu na SZ (10). Liečba BB znížila ročné riziko celkovej mortality v ESC-HF Pilot Survey u pacientov s chronickým SZ (bez selekcie podľa EFĽK) o 50 % a liečba ACEI/ARB o 32 % (3).

Preskripcia ivabradínu u pacientov s HFrEF je na Slovensku vysoká – 39,7 %. Na porovnanie v španielskom subregistri veľkého registra ESC HF-LT dostalo ivabradín 29,1 % pacientov, ktorí mohli mať z neho benefit (8). V geograficky blízkom aktuálnom nemeckom registri REFLECT-HF (384 pacientov s EFĽK ≤ 35 %, NYHA II – IV) nedostal ivabradín žiadny pacient v triede NYHA II a len 10,3 % v triede NYHA III – IV (11). Autori registra uvádzajú, že je to v rozpore so známym faktom, že len 30 – 35 % pacientov s HFrEF dosiahne cieľovú hodnotu srdcovej frekvencie samotnými BB. Nízky podiel pacientov liečených ivabradínom považujú za výrazný hendikep. Vysoký podiel pacientov na liečbe ivabradínom v registri EPIT-HF iste súvisí s vysokým podielom závažne symptomatického HFrEF (NYHA III + IV 51,7 %) a priemernou srdcovou frekvenciou 73,5/min. Prekvapivým výsledkom nášho prieskumu je vysoký podiel pacientov, ktorí mali kombináciu ivabradín + BB – 35,6 %. Celkový podiel pacientov na liečbe ivabradínom bol 39,7 %. „Monoterapia“ ivabradínom bez BB je podľa toho veľmi nízka – 4,1 % pacientov. Tento podiel je prekvapivo nízky už len v porovnaní so známou pomerne vysokou prevalenciou pacientov s HFrEF, ktorí majú významnú hypotenziu a BB sú u nich kontraindikované (9).

at least as good in Slovakia as in the developed countries over the last ten years: BB 92% vs 78-97%, ACEI/ARB 93% vs 80-93%, MRA 80% vs 18-68%, ACEI/ARB + BB 86% vs. 61-79%.

Given these values, the estimated gaps in ACEI/ARB and BB therapy for HFrEF are not big. True undertreatment is reported for ACEI/ARB 3.2-13.1% and for BB 1.8-3.9% (1, 8, 9). Higher undertreatment is known for MRA – 5.4-16.8% (1, 8, 9). Insufficient adherence to ACEI/ARB, BB, and MRA therapy increases 2.2-2.3-fold all-cause mortality and cardiovascular mortality in HFrEF patients (10). BB treatment reduced the risk of all-cause mortality in ESC-HF Pilot Survey (unselected patients according to LVEF) by 50% and ACEI/ARB treatment by 32% (3).

Prescription of ivabradine in EPIT-HF patients with HFrEF was high – 39.7%. For comparison in the Spanish subgroup of the ESC HF Long-Term registry, ivabradine was received by 29.1% of patients who could benefit from it (8). In the geographically close current German REFLECT-HF registry (384 patients with HF and LVEF ≤ 35%), none of the patients in NYHA II class and only 10.3% of patients in NYHA III-IV classes received ivabradine (11). The authors report that this is in contradiction with the well-known fact that only 30-35% of HFrEF patients reach the target heart rate with BB alone. They consider the low proportion of patients treated with ivabradine as a significant handicap. The high proportion of ivabradine therapy in the EPIT-HF survey is certainly associated with a high proportion of HFrEF patients with severe symptomatology (NYHA classes III/IV 51.7%) and with an average heart rate of 73.5 bpm. The surprising finding of our study is the high proportion of patients who had ivabradine combined with BB – 35.6%. The overall proportion of patients treated with ivabradine in HFrEF was 39.7%. Therefore monotherapy with ivabradine without BB was infrequent – 4.1% of patients. This

Preskripcia diuretík je na Slovensku vysoká – kľučkové diuretikum 90 %, tiazidy 12 %. V literatúre je v súboroch nad 1 000 pacientov tento podiel nižší: diuretiká všeobecne 61 – 83 % (4, 12, 13), respektíve kľučkové diuretiká 64 % – 82 % (14, 15). Predpokladáme, že aj v tomto prípade bude hlavným zdôvodnením vysoký podiel závažne symptomatických pacientov.

Podiel pacientov s HFrEF, liečených srdcovými glykozidmi, kolíše v literatúre v relatívne širokom rozpätí 8 – 29 % (12 – 16). V našom prieskume bola preskripcia pomerne vysoká – 24,8 %. Zodpovedá vysokej prevalencii fibrilácie/flutteru predsiení – 38,2 %.

V literatúre existuje všeobecná zhoda, že limitujúcimi faktormi optimálnej farmakoterapie pri HFrEF sú vyšší vek a ženské pohlavie (1, 11, 17).

Všeobecne možno konštatovať, že farmakoterapia všetkými liekovými skupinami je pri HFrEF na Slovensku minimálne rovnako dobrá ako vo vyspelých krajinách. Rezervy však máme v elektroimpulzoterapii. Podiel pacientov s resynchronizačnou liečbou bol v našom prieskume 10,9 % (CRT-D 8,2 %, CRT-P 2,7 %). V nemeckom registri REFLECT-HF bol podiel v triede NYHA II 12,5 % a v triedach NYHA III – IV 14,9 %, t. j. 13,9 % všetkých pacientov (11), v španielskom registri 17,2 % (8), na rozdiel od toho vo veľkom poľskom registri len 5 % (14). Lepšie postavenie máme pri implantácii ICD (bez resynchronizačnej funkcie). V našom súbore bol podiel 16,2 %. Na porovnanie uvádzame údaje z európskych registrov: Švajčiarsko 5,5 % (18), Nemecko 4,9 % (pacienti v triede NYHA III – IV) (11), Poľsko 10 % (14), Španielsko 32,4 % (8). Relatívne nižší podiel implantácií ICD vo vyspelých európskych krajinách možno pravdepodobne vysvetliť faktom, že namiesto ICD volia priamo CRT-D.

Liečba HFpEF a HFmrEF

Definícia HFpEF bola v minulosti nejednotná. Jestvujú údaje o liečbe pacientov s HFpEF a EF ĽK ≥ 40 % – registre ADHERE-US a ADHERE-I (19), Israel Nationalwide HF Survey (20), respektíve pri EFĽK > 45 % – register ESC HF-LT (9). Podľa aktuálnej definície ESC je HFpEF definované hodnotou EF ĽK ≥ 50 % (1). Pri tejto definícii máme k dispozícii len obmedzený rozsah informácií o liečbe (oproti pacientom s HFrEF). Porovnanie publikovaných údajov s výsledkami EPIT-HF je v **tabuľke 4a**. Analogicky ako pri HFrEF je prevalencia liečby základnými liekovými skupinami (BB, ACEI/ARB, MRA) na Slovensku rovnaká alebo vyššia ako v literatúre. To isté platí aj o pacientoch s HFmrEF **(tabuľka 4b)**.

Kľučkové diuretiká sa u našich pacientov s HFpEF indikujú významne v menšej miere ako pri HFrEF – 55 %. Predpokladáme, že to zodpovedá nižšej miere manifestnej kongescie a významne nižšiemu podielu pacientov v triedach NYHA III a IV. Na rozdiel od toho tiazidy sa používajú

proportion is surprisingly low compared to the known relatively high prevalence of patients with HFrEF having significant hypotension and contraindication of BB (9).

Prescription of diuretics in our HFrEF patients was high – loop diuretics 90%, thiazides 12%. In the study groups with HFrEF over 1 000 patients this proportion was lower: unspecified diuretics 61-83% (4, 12, 13) and loop diuretics 64%-82% (14, 15). We assume that even in this case, the high proportion of severely symptomatic patients in EPIT-HF can be the main explanation.

The proportion of patients with HFrEF treated with cardiac glycosides fluctuates in literature in a relatively wide range of 8-29% (12-16). The prescription in our survey was relatively high – 24.8%. This corresponds with a high prevalence of the atrial fibrillation / atrial flutter (38%).

There is general agreement in the literature that the limiting factors for optimal medical treatment in HFrEF are higher age and female gender (1, 11, 17).

In general, the proportion of pharmacotherapy for HFrEF with all drug classes is at least as good in Slovakia as in the high-income countries. However, fewer patients received CRT-D and CRT-P – 8.2% and 2.7%, respectively. In the German REFLECT-HF registry, the proportion of patients with implanted CRT was 12.5% in the NYHA II class and 14.9% in the NYHA III-IV classes, i.e. 13.9% of all patients (11). In the Spanish subgroup of the ESC HF Long-Term registry 17.2% of patients fulfilling the criteria for resynchronization therapy have received the CRT device (8). By contrast, only 5% of patients with HFrEF received CRT in the large Polish DATA-HELP registry. A relatively better share was recorded in EPIT-HF survey for ICD implantation (without resynchronization function) – 16.2%. For comparison, we report data from European registries: Switzerland 5.5% (18), Germany 4.9% (11), Poland 10% (14), Spain 32.4% (8). A relatively lower proportion of ICD implants in some developed European countries may be explained by the fact that CRT-D was prefered instead of ICD.

Therapy for HFpEF and HFmrEF

The HFpEF definition was inconsistent in the past. There are data on the treatment of patients with HFpEF and LVEF ≥ 40% from the ADHERE-US and ADHERE-I registries (19), the Israel Nationalwide HF Survey (20) or with LVEF > 45% from the ESC HF Long-Term registry (9). According to the current definition of ESC, HFpEF is defined by LVEF ≥ 50% (1). With this definition, we have only a limited range of information on the treatment of HFpEF (compared to patients with HFrEF). Comparison of published data with EPIT-HF results is shown in **Table 4a**.

Similarly to HFrEF, the prevalence of baseline drug therapy (BB, ACEI/ARB, MRA) in Slovakia is the same or higher than in the literature. The same applies to patients with HFmrEF **(Table 4b)**.

Table 4a Prevalence of treatment with beta-blockers, ACEI/ARB and MRA in patients with HFpEF
Tabuľka 4a *Prevalencia liečby betablokátormi, ACEI/ARB a MRA u pacientov s HFpEF*

Authors *(Autori)*	n	Type *(Typ)*	BB	ACEI/ARB	MRA	ACEI/ARB + BB
Fonarow[21] (2007)	10 072	OPTIMIZE-HF registry	57%	44% ACEI 14% ARB	7%	-
Tsuji[22] (2017)	2 154	CHART-2 trial	46.4%	42.2% ACEI 34.1% ARB	19.4%	-
Pascual-Figal[15] (2017)	635*	REDINSCOR I, MUSIC registries	59.7%	78.9%	29.0%	-
Rickenbacher[18] (2017)	112	TIME-CHF trial	69.6%	86.6%	25.0%	-
Dubrava (2018)	788*	EPIT-HF survey	83.4%	87.7%	28.9%	73.9%

Table 4b Prevalence of treatment with beta-blockers, ACEI/ARB and MRA in patients with HFmrEF
Tabuľka 4b *Prevalencia liečby betablokátormi, ACEI/ARB a MRA u pacientov s HFmrEF*

Authors *(Autori)*	n	Type *(Typ)*	BB	ACEI/ARB	MRA	ACEI/ARB + BB
Fonarow[21] (2007)	7 321	OPTIMIZE-HF registry	66%	52% ACEI 12% ARB	10%	-
Tsuji[22] (2017)	596	CHART-2 trial	63.8%	51% ACEI 29% ARB	29.3%	-
Pascual-Figal[15] (2017)	460*	REDINSCOR I, MUSIC registries	76.7%	87.2%	40.0%	-
Rickenbacher[18] (2017)	108	TIME-CHF trial	73.1%	90.7%	33.3%	-
Dubrava (2018)	720*	EPIT-HF survey	90.4%	92.9%	55.4%	84.7%

Legend as in Table 3 *(legenda ako v tabuľke 3)*. HFpEF – heart failure with preserved ejection fraction *(srdcové zlyhávanie so zachovanou ejekčnou frakciou)*, HFmrEF – heart failure with mid-range ejection fraction *(srdcové zlyhávanie s mid-range ejekčnou frakciou)*

významne častejšie ako pri HFrEF – 29 %. V literatúre sa podiel pacientov s HFpEF liečených diuretikami uvádza 52 – 91 % (15, 18, 21, 22). Podiel liečby kľučkovými diuretikami aj tiazidmi sa u našich pacientov s HFmrEF nachádza medzi HFrEF a HFpEF, čo zodpovedá „intermediárnemu" podielu prevalencie pokročilých funkčných štádií NYHA III + IV medzi ich prevalenciou u pacientov s HFrEF a HFpEF. Podiel pacientov s HFmrEF s diuretickou liečbou sa uvádza 63 – 90 % (15, 18, 21, 22).

Prevalencia našich pacientov s HFpEF a HFmrEF liečených srdcovými glykozidmi (12,7 %, respektíve 15,8 %) je v porovnaní s prevalenciou fibrilácie/flutteru predsiení (38,8 %, respektíve 41,3 %) pomerne nízka, ale porovnateľná s literatúrou (18, 21, 22).

Ivabradín nemá registrovanú indikáciu v liečbe HFpEF ani HFmrEF. Podiel našich pacientov s HFpEF, respektíve HFmrEF, ktorí sú liečení ivabradínom – 28,1 %, respektíve 34,7 %, je preto zdanlivo prekvapivo vysoký. Existujú dve potencionálne vysvetlenia: 1. Ivabradín bol pôvodne indikovaný pri HFrEF. V dôsledku priaznivého efektu liečby došlo k tranzícii do jednej z dvoch skupín s vyššou EFĽK. 2. Ivabradín bol primárne indikovaný pre stabilnú angínu pektoris. Rovnako ako pri HFrEF, dominantný podiel pacientov má ivabradín v liečbe súbežne s BB (21,6 %, respektíve 30,8 %). Na Slovensku je globálne vysoký podiel liečby ivabradínom pri SZ. Na porovnanie v registri ESC HF-LT (EFĽK > 45 %) sa indikoval ivabradín u 4,9 % pacientov (9).

Všeobecne možno konštatovať, že farmakoterapia HFmrEF sa viac približovala liečbe HFrEF ako liečbe HFpEF. Na rozdiel od toho American College of Cardiology a American Heart

The loop diuretics were significantly less indicated in our HFpEF patients than in HFrEF – 55%. We assume that this corresponds to a lower proportion of congestive failure and a significantly lower proportion of patients in NYHA class III/IV. Thiazides, on the other hand, were used significantly more frequently than in HFrEF – 29%. In the literature, the proportion of patients with HFpEF treated with diuretics is 52-91% (15, 18, 21, 22). The rate of loop diuretics and thiazide treatment in our patients with HFmrEF was between the rates in HFrEF and HFpEF. This corresponds to the intermediate prevalence of advanced NYHA class III/IV compared to patients with HFrEF and HFpEF. The proportion of patients with HFmrEF treated with diuretics is 63-90% in the literature (15, 18, 21, 22).

The prevalence of our patients with HFpEF and HFmrEF treated with cardiac glycosides (12.7% and 15.8%) is relatively low compared to the prevalence of atrial fibrillation/atrial flutter (38.8% and 41.3%, respectively) but it is comparable with the literature data (18, 21, 22).

Ivabradine has no registered indication in the treatment of HFpEF or HFmrEF. The proportion of our patients with HFpEF, or HFmrEF treated with ivabradine (28.1% and 34.7%), is therefore apparently high. There are two potential explanations: 1. ivabradine was originally indicated for HFrEF. Due to the beneficial effect of the treatment, the patient has transitioned to one of two HF phenotypes with higher LVEF, 2. ivabradine was primarily indicated for stable angina pectoris. As with HFrEF, the majority of patients with HFpEF and HFmrEF received ivabradine concomitantly with BB. In Slovakia there is generally a good share of ivabradine treatment in chronic HF. For comparison in ESC HF Long-Term registry (LVEF > 45%), ivabradine was used in 4.9% of patients (9).

Association uvádzajú, že charakteristiky, liečba a prognóza pacientov so SZ a EFĽK 41 – 49 % sa zdá byť podobná pacientom s HFpEF (23).

Elektroimpulzoterapia SZ nemá pri HFpEF ani pri HFmrEF indikáciu per se s výnimkou implantácie ICD v sekundárnej prevencii náhlej srdcovej smrti. Preto neprekvapuje len minimálny podiel našich pacientov s oboma fenotypmi SZ, ktorí mali implantovaný CRT, respektíve ICD **(tabuľka 2)**. Ide o zhodu s literatúrou (18, 22). Dôvodom, prečo minimálny podiel našich pacientov s HFpEF a HFmrEF má špecifickú elektroimpulzoterapiu, je okrem sekundárnej prevencie opäť tranzícia z fenotypu HFrEF.

Preferencie liekov v rámci liekových skupín

Ešte podstatne menej informácií ako o používaní jednotlivých liekových skupín pri SZ máme o voľbe jednotlivých molekúl v rámci liekových skupín.

Z literatúry sú nám známe len dve práce, ktoré hodnotili preskripciu konkrétnych BB pri SZ. Go a spol. hodnotili v pomerne starej práci (pacienti hospitalizovaní pre SZ v rokoch 2001 – 2003) preskripciu BB v súbore 11 326 pacientov bez zreteľa na EF ĽK. Dominoval metoprolol (bližšie nešpecifikovaný), nasledovali atenolol a karvedilol (24). V aktuálnom registri ESC HF-LT, do ktorého boli zaradení pacienti z 21 európskych a mediteránskych krajín, dominovali u pacientov s EFĽK ≤ 45 % (n = 4 792) aj u pacientov s EFĽK > 45 % (n = 1 499) bisoprolol a karvedilol s porovnateľnou mierou preskripcie a so značným odstupom nasledoval metoprol (9). U našich pacientov pri všetkých troch fenotypoch SZ jasne dominoval bisoprolol, nasledovaný s odstupom vyše 10 % karvedilolom a metoprololom sukcinátom **(obrázok 1)**.

Pri ďalších liekových skupinách sú nám známe len výsledky z uvedeného registra ESC HF-LT (9). Rovnako ako pri BB, aj pri ACEI je poradie najviac používaných liekov na Slovensku odlišné. V registri ESC HF-LT bolo zostupné poradie preferencií ramipril, enalapril a perindopril (nezávisle od EFĽK). Naproti tomu na Slovensku je absolútne najčastejšie predpisovaným ACEI pri všetkých typoch SZ perindopril a s odstupom tiež vyše 10 % nasledujú ramipril a trandolapril **(obrázok 2)**.

Prevalencia žiadneho lieku spomedzi ARB nepresiahla v európskom registri 10 % ani v jednom podsúbore. Najviac sa používali kandesartan, valsartan a losartan, bez významnejších rozdielov medzi nimi (9). Situácia na Slovensku je diametrálne odlišná. Paradoxne sa pri všetkých typoch SZ najviac predpisuje telmisartan, ktorý však podľa SPC nemá indikáciu na liečbu SZ **(obrázok 3)**. Predpokladáme, že prioritnou indikáciou pre telmisartan bola artériová hypertenzia a nie SZ.

V prieskume EPIT-HF bol pri všetkých fenotypoch SZ súčet prevalencie pacientov liečených ACEI a prevalencie pacientov liečených ARB vyšší ako prevalencia pacientov

In general, pharmacotherapy for HFmrEF has been more closely related to HFrEF therapy than to HFpEF therapy in EPIT-HF survey. In contrast, the American College of Cardiology and the American Heart Association report that the characteristics, treatment and prognosis of patients with HF and LVEF 41-49% appear to be similar to patients with HFpEF (23).

Electroimpulse therapy (CRT-D, CRT-P, ICD) has no indication in HFpEF or HFmrEF with the exception of ICD implantation in secondary prevention of sudden cardiac death. Therefore, we are not surprised by the minimal proportion of our patients with both HF phenotypes who have had CRT or ICD implanted **(Table 2)**. There is a consistency with literature (18, 22). The reason why the minimal proportion of our patients with HFpEF and HFmrEF has specific electroimpulse therapy is, in addition to secondary prevention, again a transition from the HFrEF phenotype.

Drug preferences within drug classes

Even less information exists on the preference of individual drugs within the drug classes than on the use of the drug classes in HF phenotypes.

We found two papers that evaluated the prescription of specific BB in chronic HF. Go et al. evaluated in a relatively old study (patients hospitalized for HF in 2001-2003) the BB prescription in a group of 11 326 patients, regardless of LVEF. Metoprolol (not specified as succinate or tartrate) dominated, followed by atenolol and carvedilol (24). In the current ESC HF Long-Term registry, which included patients from 21 European and Mediterranean countries, bisoprolol and carvedilol were dominating BB in patients with LVEF ≤ 45% (n = 4 792) as well in patients with LVEF ≥ 45% (n = 1 499). Prescription of both molecules was comparable. Bisoprolol and carvedilol were followed by metoprolol with a much lower share (9). In our patients, bisoprolol was clearly the most frequently used BB in all three HF phenotypes. Carvedilol and metoprolol succinate followed, with a prescription rate more than 10% lower compared to bisoprolol **(Figure 1)**.

For other drug groups, we can compare the drug preferences only with the ESC HF Long-Term registry (9). As with BB, also in ACEI, the order of the most frequently used drugs in Slovakia is different. In the ESC HF Long-Term registry, ramipril, enalapril and perindopril (in descending order) were the most commonly used ACEI, independently from LVEF. In contrast, in Slovakia, the absolutely most frequently prescribed ACEI was perindopril in all types of HF. Ramipril and trandolapril were also commonly used but with prescription rate more than 10% lower compared to perindopril **(Figure 2)**.

The prevalence of any ARB did not exceed 10% in the European registry. The most commonly used ARB were candesartan, valsartan and losartan, with no significant differences between them (9). The situation in Slovakia is completely different. Paradoxically, telmisartan was the most prescribed

liečených ACEI a/alebo ARB. Z toho vyplýva prekvapivé zistenie, že istý podiel pacientov dostával súčasne non lege artis aj ACEI aj ARB. Konkrétne ide o 3,3 % všetkých pacientov s HFrEF, 1,5 % pacientov s HFmrEF a 4,3 % pacientov s HFpEF.

Na Slovensku existujú dve molekuly MRA na p. o. aplikáciu. Zistili sme, že pri HFrEF sa preferuje eplerenón, kým pri HFpEF a HFmrEF spironolaktón **(obrázok 4)**. V európskom registri absolútne prevažuje nezávisle od EFĽK spironolaktón oproti eplerenónu a marginálne sa používa aj kanrenón (9).

Limitácie

Diagnóza SZ nebola centrálne validovaná. Pacienti boli klasifikovaní do fenotypov SZ podľa EFĽK, ktorá mohla byť významne ovplyvnená viacerými faktormi: 1. Absencia centrálnej validácie. 2. Meranie EFĽK nebolo štandardizované. 3. Akceptovala sa posledná dostupná hodnota EFĽK (nemuselo ísť nevyhnutne o EFĽK v deň zaradenia do prieskumu ani iniciálnu hodnotu EFĽK pri stanovení diagnózy SZ). V čase realizácie prieskumu ešte neexistovala kategória HFmrEF. Túto kategóriu sme preto vytvorili v post-hoc analýze. Napriek tomu ide o prvé publikované epidemiologické údaje o týchto pacientoch na Slovensku.

Prevalencia terapie jednotlivými liekovými skupinami môže byť čiastočne ovplyvnená tranzíciou medzi fenotypmi SZ. Liečba mohla byť pôvodne indikovaná u pacienta, ktorého hodnota EFĽK a kategória SZ sa mohli v nasledujúcom období zmeniť. Zo súčasného pohľadu v prieskume chýba liečba ARNI (sakubitril/valsartan), pretože v čase realizácie ešte nebola dostupná.

Závery

Pri porovnaní liečby troch fenotypov SZ sme zistili najvýraznejšie rozdiely medzi HFrEF a HFpEF. Pri tejto komparácii bol signifikantný rozdiel v prevalencii liečby všetkými liekovými skupinami, CRT-D, CRT-P a ICD. Farmakoterapia HFmrEF sa viac približovala liečbe HFrEF ako liečbe HFpEF. Prevalencia terapie HFmrEF ľubovoľnou liekovou skupinou, respektíve CRT-D, CRT-P a ICD, bola vždy intermediárna medzi prevalenciou terapie pri HFrEF a HFpEF. Prevalencia liečby ľubovoľnou liekovou skupinou pri všetkých fenotypoch chronického SZ je na Slovensku minimálne rovnako dobrá ako v „high-income" krajinách. Preferencie jednotlivých molekúl v rámci BB, ACEI a ARB sú však na Slovensku odlišné od európskeho ESC HF Long-Term registra. Najčastejšie indikovanými liekmi sú na Slovensku pri všetkých fenotypoch SZ bisoprolol, perindopril a telmisartan.

ARB in all types of HF **(Figure 3)**. However it should be emphasized, that according to the summary of product characteristics telmisartan does not have an indication for HF treatment **(Figure 3)**. We suppose that the priority indication for telmisartan was arterial hypertension rather than HF.

In EPIT-HF, the sum of prevalences of ACEI-treated patients and of ARB-treated patients was higher than the prevalence of patients treated with ACEI and/or ARB in all HF phenotypes. Therefore, it is obvious that a certain proportion of patients received non lege artis both ACEI and ARB (3.3%, 1.5% and 4.3% of all patients with HFrEF, HFmrEF and HFpEF, respectively).

There are two MRA molecules in Slovakia for oral application. We have found that eplerenone was preferred for HFrEF while spironolactone for HFpEF and HFmrEF **(Figure 4)**. In the European registry, spironolactone was absolutely dominant over eplerenone, independently from LVEF. Canrenone is used only marginally (9).

Limitations

Diagnosis of HF was not centrally validated. Patients were classified into HF phenotypes according to LVEF, which could be significantly influenced by several factors: 1. absence of central validation, 2. measurement of LVEF was not standardized, 3. acceptance of the last available LVEF value (LVEF on the day of enrollment was not required). At the time of our survey, HFmrEF category was not yet defined. Therefore, we created this category only in the post-hoc analysis. However, this is the first published epidemiological data on the treatment of patients with HFmrEF in Slovakia. The prevalence of treatment by individual drug classes may be partly influenced by the transition between HF phenotypes. Treatment could initially be indicated in a patient whose LVEF and HF category could change over the next period. The data on ARNI treatment (sacubitril/valsartan) is lacking since it was not yet available at the time of EPIT-HF survey.

Conclusion

Comparing the treatment of three HF phenotypes we found the most striking difference was between HFrEF and HFpEF. In this comparison, we identified a significant difference in the prevalence of treatment for all drug classes, CRT-D, CRT-P and ICD. Pharmacotherapy for HFmrEF has been more closely related to HFrEF treatment than to HFpEF treatment. The prevalence of therapy for HFmrEF by any drug class, CRT-D, CRT-P and ICD, was always intermediate between the prevalence of therapy for HFrEF and HFpEF.

The prevalence of treatment with any drug class in all HF phenotypes was at least as good in Slovakia as in the high-income countries. The drug preferences within BB, ACEI and ARB classes were different in EPIT-HF survey from those in

Autori

Obaja autori sa významne podieľali na štúdii. JD naplánoval štúdiu a vytvoril jej dizajn, zodpovedal za zber údajov a napísal rukopis. RŠ vykonal štatistickú analýzu a revidoval rukopis.

Poďakovanie

Ďakujeme všetkým 161 participujúcim lekárom za podporu projektu EPIT-HF a aktívnu účasť na zbere údajov.

Konflikt záujmov

Autori deklarujú, že neexistuje žiadny konflikt záujmov vo vzťahu k tejto práci.

Podpora projektu

Projekt EPIT-HF bol podporený edukačným grantom spoločnosti Servier Slovakia.

the ESC HF Long-Term registry. The most commonly indicated drugs within these drug classes in Slovakia were bisoprolol, perindopril and telmisartan for all phenotypes of HF.

Contributors

All authors have contributed substantially the body of work. JD planned and designed the study, carried out data collection and wrote the manuscript. RS undertook the statistical analysis and revised the manuscript for submission.

Acknowledgements

We express our gratitude to all 161 participating physicians for supporting EPIT-HF project and their activity in data collection.

Conflict of interest

None declared.

Funding

EPIT-HF survey was supported by the educational grant of Servier Slovakia.

Literatúra/References

1. Ponikowski P, Voors AA, Anker SD, et al.2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37(27):2129-200.
2. Crespo-Leiro MG, Anker SD, Maggioni AP, et al. European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT): 1-year follow-up outcomes and differences across regions. Eur J Heart Fail 2016;18(6):613-625.
3. Maggioni AP, Dahlström U, Filippatos G, et al. EURObservational Research Programme: regional differences and 1-year follow-up results of the Heart Failure Pilot Survey (ESC-HF Pilot). Eur J Heart Fail 2013;15(7):808-817.
4. de Groote P, Isnard R, Assyag P, et al. Is the gap between guidelines and clinical practice in heart failure treatment being filled? Insights from the IMPACT RECO survey. Eur J Heart Fail 2007;9(12):1205-1211.
5. Alhabeeb W, Elasfar A, AlBackr H, et al. Clinical characteristics, management and outcomes of patients with chronic heart failure: Results from the heart function assessment registry trial in Saudi Arabia (HEARTS-chronic). Int J Cardiol 2017;235:94-99.
6. Cenkerová K, Dúbrava J, Kalužay J, et al. Epidemiológia „diastolického" srdcového zlyhávania. Klinické charakteristiky a komparácia so systolickým srdcovým zlyhávaním. Kardiol Prax 2012;10(2):55-63.
7. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2012;14(8):803-869.
8. Crespo-Leiro MG, Segovia-Cubero J, González-Costello J, et al. Adherence to the ESC Heart Failure Treatment Guidelines in Spain: ESC Heart Failure Long-term Registry. Rev Esp Cardiol (Engl Ed) 2015;68(9):785-793.
9. Maggioni AP, Anker SD, Dahlström U, et al. Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12,440 patients of the ESC Heart Failure Long-Term Registry. Eur J Heart Fail 2013;15(10):1173-1184.
10. Komajda M, Cowie MR, Tavazzi L, et al. Physicians' guideline adherence is associated with better prognosis in outpatients with heart failure with reduced ejection fraction: the QUALIFY international registry. Eur J Heart Fail 2017 Apr 30. doi: 10.1002/ejhf.887. [Epub ahead of print]
11. Böhm M, Tschöpe C, Wirtz JH, et al. Treatment of heart failure in real-world clinical practice: findings from the REFLECT-HF registry in patients with NYHA class II symptoms and a reduced ejection fraction. Clin Cardiol 2015;38(4):200-207.
12. Zugck C, Martinka P, Stöckl G. Ivabradine treatment in a chronic heart failure patient cohort: symptom reduction and improvement in quality of life in clinical practice. Adv Ther 2014;31(9):961-974.
13. von Scheidt W, Zugck C, Pauschinger M, et al. Characteristics, management modalities and outcome in chronic systolic heart failure patients treated in tertiary care centers: results from the EVIdence based TreAtment in Heart Failure (EVITA-HF) registry. Clin Res Cardiol 2014;103(12):1006-1014.

14. Jankowska EA, Kalicinska E, Drozd M, et al. Comparison of clinical profile and management of outpatients with heart failure with reduced left ventricular ejection fraction treated by general practitioners and cardiologists in contemporary Poland: the results from the DATA-HELP registry. Int J Cardiol 2014;176(3):852-858.
15. Pascual-Figal DA, Ferrero-Gregori A, Gomez-Otero I, et al. Mid-range left ventricular ejection fraction: Clinical profile and cause of death in ambulatory patients with chronic heart failure. Int J Cardiol 2017;240:265-270.
16. Tsuchihashi-Makaya M, Hamaguchi S, Kinugawa S, et al. Characteristics and outcomes of hospitalized patients with heart failure and reduced vs preserved ejection fraction. Report from the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD). Circ J 2009;73(10):1893-1900.
17. Yancy CW, Fonarow GC, Albert NM, et al. Influence of patient age and sex on delivery of guideline-recommended heart failure care in the outpatient cardiology practice setting: findings from IMPROVE HF. Am Heart J 2009;157(4):754-62.e2.
18. Rickenbacher P, Kaufmann BA, Maeder MT, et al. Heart failure with mid-range ejection fraction: a distinct clinical entity? Insights from the Trial of Intensified versus standard Medical therapy in Elderly patients with Congestive Heart Failure (TIME-CHF). Eur J Heart Fail 2017 Mar 15. doi: 10.1002/ejhf.798. [Epub ahead of print]
19. West R, Liang L, Fonarow GC, et al. Characterization of heart failure patients with preserved ejection fraction: a comparison between ADHERE-US registry and ADHERE-International registry. Eur J Heart Fail 2011;13(9):945-952.
20. Lewis BS, Shotan A, Gottlieb S, et al. Late mortality and determinants in patients with heart failure and preserved systolic left ventricular function: the Israel Nationwide Heart Failure Survey. Isr Med Assoc J 2007;9(4):234-238.
21. Fonarow GC, Stough WG, Abraham WT, et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. J Am Coll Cardiol 2007;50(8):768-777.
22. Tsuji K, Sakata Y, Nochioka K, et al. Characterization of heart failure patients with mid-range left ventricular ejection fraction-a report from the CHART-2 Study. Eur J Heart Fail 2017;19(10):1258-1269.
23. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;62(16):e147-239.
24. Go AS, Yang J, Gurwitz JH, et al. Comparative effectiveness of different beta-adrenergic antagonists on mortality among adults with heart failure in clinical practice. Arch Intern Med 2008;168(22):2415-2421.
25. Fonarow GC, Yancy CW, Albert NM, et al.Heart failure care in the outpatient cardiology practice setting: findings from IMPROVE HF. Circ Heart Fail 2008;1(2):98-106.
26. Peterson PN, Chan PS, Spertus JA, et al. Practice-level variation in use of recommended medications among outpatients with heart failure: Insights from the NCDR PINNACLE program. Circ Heart Fail 2013;6(6):1132-1138.
27. Chioncel O, Lainscak M, Seferovic PM, et al. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry. Eur J Heart Fail 2017 Apr 6. doi: 10.1002/ejhf.813. [Epub ahead of print]
28. Chin KL, Skiba M, Tonkin A, et al. The treatment gap in patients with chronic systolic heart failure: a systematic review of evidence-based prescribing in practice. Heart Fail Rev 2016;21(6):675-697.