A comparison of heart failure patients with reduced ejection fraction in the Moravian Midlands Registry with the LCZ696 patients in the Paradigm-HF trial

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Background and Aims. There are limited data on real clinical practice in heart failure patients in the Czech Republic. We analysed the clinical parameters from the Moravian Midlands Registry (MMR) and compared them to LCZ696 patients in the Paradigm-HF trial. The Moravian Midlands Registry is a retrospective patient database from two outpatient cardiology centres in the Czech Republic. The Paradigm-HF is a large-scale prospective randomized multicentre trial with more than 8000 individuals with stabilized chronic heart failure.

Methods. A retrospective analysis of heart failure with reduced ejection fraction patients from two outpatient cardiology centres in the Czech Republic from October 2016 to December 2019.

Results. Patients in the MMR were younger (60.5 ± 10.7 vs 63.8 ± 11.5 years, $P<0.05$), had a higher body mass index (30.3 ± 5.0 vs 28.1 ± 5.5, $P<0.05$) and higher serum creatinine level (101.9 ± 36.0 vs 99.9 ± 26.5 μmol/L, $P<0.05$). MMR patients had lower left ventricular ejection fraction (27.8 ± 6.9 vs 29.6 ± 6.1%, $P<0.05$). The serum N-terminal pro-B-type natriuretic peptide, [2563.5 (377–3536) vs 1631 (885–3154), was non significantly higher $P=0.07$]. Pharmacotherapy use differed for mineralocorticoid antagonist (91.4% in MMR vs 54.2% in Paradigm-HF), and digoxin (13.5% vs 29.2%). Beta-blocker use was similar (96.2% vs 93.1%) as was angiotensin-converting enzyme (ACE) inhibitors – (71.2% vs 78.0%) and angiotensin-receptor blockers – ARB (27.9% vs 22.2%). Dosages of the commonly used ACE inhibitors at the screening visit (Paradigm-HF) / before angiotensin receptor-neprilysin inhibitor administration (MMR) differed significantly only for ramipril (7.0 ± 3.1 mg vs 4.8 ± 2.9 mg, $P<0.05$), dosages of ARB were – losartan (67.1 ± 30.2 vs 39.6 ± 32.0 mg, $P=0.09$) and valsartan (181.5 ± 71.1 vs 130.9 ± 82.2 mg, $P=0.07$). There was a substantial difference in device-based therapy (ICD in 60.6%, CRT 25.9% in MMR vs 14.9% and 7.0% in Paradigm-HF).

Conclusion. The differences between the groups for the majority of clinical parameters compared were minimal, except for younger age, higher body mass index and serum creatinine level and lower left ventricular ejection fraction and substantially lower dosage of administered ramipril prior to commencing sacubitril/valsartan therapy. There was a higher prevalence of implantable cardioverter-defibrillators (ICD) and cardiac resynchronization therapy (CRT) in the MMR group.

Key words: heart failure, heart failure with reduced ejection fraction, treatment, sacubitril-valsartan, registry, MMR, Paradigm HF

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INTRODUCTION

Heart failure (HF) remains a substantial healthcare and socioeconomic issue despite the phenomenal advances in diagnostic strategies and cardiovascular pharmacotherapy in recent decades. The incidence and prevalence of heart failure based on data from the Czech National Registry of Reimbursed Health Services in 2018 was 551 persons per 100 000 population and 2689 persons per 100 000 population respectively[1]. The same study found stable incidence of heart failure but increasing prevalence. The prevalence of HF in persons over 60 years of age is greater than 10% (ref.[2]). Patients with heart failure with reduced ejection fraction (HFrEF) represent 60% of all heart failure patients. Patients with mildly reduced ejection fraction (HFmrEF) represent 24% and 16% of patients have heart failure with preserved ejection fraction (HFpEF) (ref.[3]). The one-year mortality as per the ESC-HF Long Term Registry in HFrEF patients is 8.8%, in HFmrEF patients 7.6% and in HFpEF patients 6.3%. The one-year mortality based on data from the Czech National Registry of Reimbursed Health Services in all heart failure patients was 15.9%. The FAR-NHL registry reported a two-year mortality of 12.1% (ref.[4]). Although mortality is still high, it has improved due to advances in heart failure therapy[5]. Updates on heart failure is systematically documented by the two most important professional societies, the European Society of Cardiology and the American College of Cardiology/American Heart Association[6,7].

Study aim

The aim of this study was to analyse the baseline characteristics, medical history, clinical features of heart failure and therapy of heart failure patients with reduced ejection fraction in the Moravian Midlands Registry in comparison with the LCZ696 patients in the Paradigm-HF trial[8].

METHODS

The Moravian Midlands Registry is a retrospective patient database from two outpatient cardiology centres in the Czech Republic. Most patients (84 patients) in the registry derive from the Heart Failure Outpatient Clinic of the Department of Internal Medicine I – Cardiology University Hospital Olomouc. This group represents a highly specialized Heart Failure Clinic in a tertiary medical centre. The minority (20 patients) derive from the ambulatory general cardiology practice in Svitavy District Hospital. The time period in the MMR registry was October 2016 to December 2019. The time period of the Paradigm-HF Study was December 2009 to November 2012. Inclusion criteria for patients in the MMR registry were identical to the Paradigm-HF LCZ696 patient group except for the absence of cut-off levels of serum level of N-terminal pro-B-type natriuretic peptide. Exclusion criteria were identical for both groups except for the obligation of mineralocorticoid receptor inhibitors administration in MMR patients.

Statistics

For the dataset's statistical evaluation, the Paradigm HF study methodology was used. An aligned statistical approach was used to allow an easy comparison of baseline characteristics of MMR patients with previous studies. Continuous variables are reported as means ± standard deviation. The difference between groups were compared using unpaired t-test that assumed unequal variance between groups. Statistical significance was defined as $P<0.05$. The p-value could be calculated for continuous variables only.

Categorical variables are reported as an absolute number and percentages. Percentages may not total 100 because of rounding. Unless otherwise specified, the total number of records is 104.

Table 1. Characteristics of the patients at baseline.

Characteristic	Paradigm HF LCZ696 (n=4187)	MMR (n=104)
Age – yr	63.8 ± 11.5	60.5 ± 10.7
Female sex – no. (%)	879 (21.0)	17 (16.3)
Race or ethnic group – no. (%)		
White	2763 (66.0)	104 (100)
Region – no. (%)		
Central Europe	1393 (33.3)	104 (100)
Systolic blood pressure – mm Hg	122 ± 15	124.8 ± 20.8
Heart rate – beats/min	72 ± 12	73.5 ± 12.7
Body-mass index	28.1 ± 5.5	30.3 ± 5.0
Serum creatinine – μmol/L	99.9 ± 26.5	101.9 ± 36.0*
Clinical features of heart failure		
Ischemic cardiomyopathy – no. (%)	2506 (59.9)	51 (49.0)
Left ventricular ejection fraction –%	29.6 ± 6.1	27.8 ± 6.9**
Median N-terminal pro-B-type natriuretic peptide (IQR) – pg/mL	1631 (885–3154)	2563.5 (377–3536)***
NYHA functional class – no. (%)		
I	180 (4.3)	5 (4.8)
II	2998 (71.6)	62 (59.6)
III	969 (23.1)	34 (32.7)
IV	33 (0.8)	3 (2.9)
Missing data	7 (0.2)	N/A
Medical history – no. (%)		
Arterial hypertension	2969 (70.9)	66 (63.5)
Diabetes mellitus	1451 (34.7)	35 (33.7)
Atrial fibrillation	1517 (36.2)	36 (34.6)
Hospitalization for heart failure	2607 (62.3)	31 (29.8)
Myocardial infarction	1818 (43.4)	49 (47.1)
Stroke	355 (8.5)	10 (9.6)

Plus–minus values are means ±SD.

*out of 102; **out of 67; ***out of 82; IQR, interquartile range; NYHA, New York Heart Association; MMR, Moravian Midlands Registry; N/A, not applicable; yr, year.

Table 2. Comparison of therapy.

	Paradigm-HF Trial LCZ696 group	MMR
Pharmacotherapy – no. (%)		
Beta-blocker	3899 (93.1)	100 (96.2)
ACE inhibitor	3266 (78.0)	74 (71.2)
ARB	929 (22.2)	29 (27.9)
Mineralocorticoid antagonist	2271 (54.2)	95 (91.4)
Diuretic	3363 (80.3)	82 (78.9)
Digitalis	1223 (29.2)	14 (13.5)
Non-pharmacological therapy – no. (%)		
Implantable cardioverter–defibrillator	623 (14.9)	63 (60.6)
Cardiac resynchronization therapy	292 (7.0)	27 (25.9)

Four most commonly used ACE inhibitors at the screening visit (Paradigm-HF) / before administration ARNI (MMR)

	Paradigm-HF Trial LCZ696 group		MMR	
	no. (%)	mean (±SD) daily dose (mg)	no. (%)	mean (±SD) daily dose (mg)
Enalapril	2185 (26.0)	16.4 ± 8.3	N/A	N/A
Ramipril	1871 (22.3)	7.0 ± 3.1	42 (40.4)	4.8 ± 2.9
Perindopril	1118 (13.3)	5.9 ± 2.7	28 (26.9)	6.3 ± 3.1
Lisinopril	576 (6.9)	18.2 ± 12.1	N/A	N/A

Four most commonly used ARBs inhibitors at the screening visit (Paradigm-HF) / before administration ARNI (MMR)

	Paradigm-HF Trial LCZ696 group		MMR	
	no. (%)	mean (±SD) daily dose (mg)	no. (%)	mean (±SD) daily dose (mg)
Losartan	791 (9.4)	67.1 ± 30.2	6 (5.8)	39.6 ± 32.0
Valsartan	397 (4.7)	181.5 ± 71.1	11 (10.6)	130.9 ± 82.2
Telmisartan	196 (2.3)	60.1 ± 23.9	9 (8.7)	62.2 ± 21.1
Candesartan	188 (2.2)	20.0 ± 9.6	1 (1)	4*

*dose of a single patient. mean or SD cannot be calculated; ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blockers; ARNI, Angiotensin Receptor-Neprilysin Inhibitor; MMR, Moravian Midlands Registry; N/A, not applicable.

RESULTS

Patients in MMR were younger (60.5 ± 10.7 vs 63.8 ± 11.5 year, $P<0.05$), with higher body mass index (30.3 ± 5.0 vs 28.1 ± 5.5, $P<0.05$) and higher serum creatinine level (101.9 ± 36.0 vs 99.9 ± 26.5 μmol/L, $P<0.05$). In the MMR, patients had lower left ventricular ejection fraction (27.8 ± 6.9 vs 29.6 ± 6.1%, $P<0.05$) with a tendency towards higher serum N-terminal pro-B-type natriuretic peptide, [2563.5 (377–3536) vs 1631 (885–3154), $P=0.07$]. There is significantly lower dosage of administered ACEi – ramipril (7.0 ± 3.1 mg vs 4.8 ± 2.9 mg, $P<0.05$) prior to commencing sacubitril/valsartan therapy together with tendency to lower dosages of ARB – losartan, valsartan.

DISCUSSION

Baseline characteristics, medical history

Patients in the Moravian Midlands Registry (MMR) were younger (60.5 ± 10.7 vs 63.8 ± 11.5 year, $P<0.05$), with a higher body mass index (30.3 ± 5.0 vs 28.1 ± 5.5, $P<0.05$) and higher serum creatinine level (101.9 ± 36.0 vs 99.9 ± 26.5 μmol/L, $P<0.05$). We calculated the mean age of patients with ischaemic cardiomyopathy in MMR registry and found it similar to the age of Paradigm-HF Study patients (63.8 ± 9.4 vs 63.8 ± 11.5). Patients with non-ischaemic cardiomyopathy in MMR registry were younger (57.2 ± 11.0, $P<0.05$) which might explain lower mean of age of all MMR patients comparing to Paradigm-HF LCZ696 group of patients.

The prevalence of diabetes mellitus (33.7% in MMR vs 34.7% in Paradigm-HF) and atrial fibrillation (34.6% in MMR vs 36.2% in Paradigm-HF) was similar. The only nationwide data report prevalence of diabetes mellitus in heart failure population is 41% (ref.[9]). Diagnosis of arterial hypertension and prior hospitalization for heart failure was less frequent in MMR patients than in Paradigm-HF group based on medical history.

The national prevalence, obtained from the Czech National Registry of Reimbursed Health Services, was higher for arterial hypertension (92.6%), atrial fibrillation (49.7%), diabetes mellitus (41%) and stroke (17.6%) (ref.[1]).

Table 3. The *P*-value calculated for continuous variables only.

	Paradigm HF LCZ696 (n=4187)	MMR (n=104)	*P*
Age – years	63.8 ± 11.5	60.5 ± 10.7	0.002
Systolic blood pressure – mm Hg	122 ± 15	124.8 ± 20.8	0.17
Heart rate – beats/min	72 ± 12	73.5 ± 12.7	0.24
Body-mass index kg/m2	28.1 ± 5.5	30.3 ± 5.0	0.00002
Serum creatinine – μmol/L	99.9 ± 26.5	101.9 ± 36.0*	0.00004
Left ventricular ejection fraction – %	29.6 ± 6.1	27.8 ± 6.9**	0.04
Median N-terminal pro–B-type natriuretic peptide (IQR) – pg/mL	1631 (885–3154)	2563.5 (376.8–3535.8)***	0.07
Ramipril – daily dose in mg	7.0 ± 3.1	4.8 ± 2.9	0.00002
Losartan – daily dose in mg	67.1 ± 30.2	39.6 ± 32.0	0.09
Valsartan – daily dose in mg	181.5 ± 71.1	130.9 ± 82.2	0.07
Telmisartan – daily dose in mg	60.1 ± 23.9	62.2 ± 21.1	0.77

*out of 102; **out of 67; ***out of 82; IQR, interquartile range; MMR, Moravian Midlands Registry.

Table 4. Four most commonly used betablockers before administration ARNI (MMR).

	no. (%)	Mean (±SD) daily dose (mg)	Minimal dose	Maximal dose
Metoprolol	45(43.3)	87.11 ± 64.43	12.5	300
Carvedilol	30 (28.8)	29.98 ± 20.53	3.13	75
Bisoprolol	23 (22.1)	6.25 ± 4.05	1.25	15
Nebivolol	1	5	N/A	N/A

ARNI, Angiotensin Receptor-Neprilysin Inhibitor; N/A, not applicable.

These differences might reflect the different approaches used to source data. In MMR patients we used medical records as the data source. Data from Czech National Registry of Reimbursed Health Services are based on billing data using the International Classification of Diseases (ICD-10) codes only.

The FAR-NHL (FARmacology and NeuroHumoraL activation) registry similarly finds a lower prevalence of ischaemic cardiomyopathy as in the MMR registry. This might be related to social factors of the studied populations. There is high ethanol consumption in Czech Republic. The average yearly consumption is 9.87 litres of 100% ethanol per capita based on 10-year average intake[10]. Patients in both MMR and FAR-NHL registries live in areas of presumptive high ethanol intake compared other parts of the Czech Republic. We speculate that the higher proportion of non-ischaemic cardiomyopathy could be due to dilated cardiomyopathy as a result of alcohol.

Clinical features of heart failure

Patients in MMR had a non-significantly higher concentration of median N-terminal pro-B-type natriuretic peptide 2563.5 vs 1631 pg/mL, *P*=0.07. They had lower left ventricular ejection fraction (27.8% vs 29.6%, *P*<0.05) and a higher proportion of patients in NYHA III functional class (32.7% vs 23.1%) than the Paradigm-HF trial patients. This difference is probably based on selection bias. Patients referred to both outpatient centres are in a more advanced stage of heart failure compared to less unwell patients who remain under the care of by local internists and general cardiologists.

Therapy of heart failure

Mortality and morbidity modifying pharmacotherapy use in both groups of patients is very similar. This might be a valuable argument in favour of forming a nationwide network of heart failure outpatients' centres[11]. A next step would be to assess if there are differences within the network of tertiary hospitals and of district hospitals or in free standing outpatient facilities.

The high prevalence of mineralocorticoid receptor inhibitors (MRA) could be explained by local policy factors. All patients in MMR were administered sacubitril-valsartan. Therefore, they were obliged by health insurance providers to be administered MRA except for intolerance of MRA. There were 21 (20.2%) patients on eplerenone and 74 patients (71.2%) on spironolactone. Only 9 patients had not tolerated MRA. The high prevalence of MRA could represent higher awareness of financial control from insurance providers prior to administration of sacubitril-valsartan due to its significant cost.

A further significant difference is the lower prevalence of digitalis therapy in MMR patients. We speculate it might be a result of high use of CRT therapy in combination with ablation of atrioventricular node in patients with heart failure and atrial fibrillation.

We found a striking difference in the use of implantable cardioverter-defibrillators (ICD) and cardiac resynchronization therapy (CRT). This difference might be explained by time difference of seven years in between MMR and Paradigm-HF trial patient recruitment. Secondly, Paradigm-HF trial enrolled patients from 47 countries with different healthcare systems and different

real-life possibilities for patient care. It corresponds to known data of ICD/CRT use as published in European Heart Rhythm Association (EHRA) White Book which confirms frequent use of device therapy in Czech Republic[12].

The essential difference in Paradigm-HF and MMR populations rests in the dosage of mortality/morbidity modifying medications. In MMR patients the most common ACEi were ramipril (40.4%) and perindopril (26.9%). These ACEi are also the most frequently used ACEi in the Czech Republic[13]. Interestingly the dose of ramipril in MMR patients was substantially lower than in Paradigm-HF patients whilst doses of perindopril were similar.

Valsartan (10.6%) was the most prescribed ARB followed by telmisartan (8.7%) and losartan (5.8%) in MMR registry. This differs from national data where the most prescribed ARB is telmisartan[13]. There is a tendency to lower dosages of valsartan and losartan in MMR patients, dose of telmisartan is comparable.

The most common betablocker in MMR patients was metoprolol (43.3%), followed by carvedilol (28.8%) and bisoprolol (22.1%). The FAR-NHL registry similarly found carvedilol (39.6%) and metoprolol (33.4%) as the leading betablockers[14].

Study limitations

MMR registry is based on retrospective data from electronic medical records. The number of patients in MMR registry is limited in comparison to nationwide dataset of patients with heart failure. There is a substantial difference of seven years between patient enrolment periods of the compared groups. There is minimal difference in inclusion/exclusion criteria based on local healthcare reimbursement policy factors. Results of comparison of MMR registry and Paradigm-HF LCZ696 subgroup reflect selected groups of patients with heart failure with reduced ejection fraction.

CONCLUSION

The patients in MMR are younger, with higher body mass index and serum creatinine level, lower left ventricular ejection fraction. These findings suggest more advanced heart failure than in patients in the Paradigm-HF LCZ696 subgroup. There is significantly lower dosage of administered ACEi – ramipril prior to commencing sacubitril/valsartan therapy together with tendency to lower dosages of ARB – losartan, valsartan. Lower dosages might be explained by more progressed heart failure in MMR patients. Patients in MMR registry have higher prevalence of implantable cardioverter-defibrillators (ICD) and cardiac resynchronization therapy (CRT) confirming access to advanced and financially demanding treatment options in studied region.

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