Pharmacotherapy of diabetes mellitus in patients with heart failure – a nation-wide analysis of contemporary treatment

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Aim. Retrospective national sub-analysis of antidiabetic pharmacotherapy in patients with diabetes mellitus (DM) and heart failure (HF) based on data reported to the National Register of Paid Health Services in the Czech Republic between 2012–2018.

Methodology and Results. In 2012, there were 75,022 patients with HF and DM (i.e. 42.5% of patients with HF), 6 years later 117,265 (i.e. 41.0% of HF patients in 2018). The most represented antidiabetic drug was metformin (45.6%). Of the insulins and analogues, glargine showed the largest positive trend (5.8% 2012; 14.8% 2018). Empagliflozin was the most prescribed SGLT-2 inhibitor (1.8% in 2018). A decrease in prescribing was observed for saxagliptin (0.5% 2012; 0.1% 2018) and for sulfonylurea derivates – gliclazide (13.0% 2012; 10.3% in 2018) and glimepiride (12.9% 2012; 9.0% 2018). Linagliptin was the most prescribed dipeptidyl peptidase inhibitor (0.7% 2012; 6.8% 2018).

Conclusion. In the Czech Republic, between 2012 and 2008, there was an increase in prevalence of patients with heart failure and concomitant diabetes mellitus, their proportion being similar. In correspondence with other registries, metformin was used mostly. A positive trend was observed in prescription of DDP-4 and SGLT-2 inhibitors, while there was a significant decrease in patients taking sulfonylureas.

Key words: diabetes mellitus, heart failure, pharmacotherapy, National Register of Paid Health Services (NRHZS)

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INTRODUCTION

Heart failure (HF) and diabetes mellitus (DM) are among the major diseases of civilization. Worldwide, there are an estimated 64.3 million people with HF (ref.[1]). HF is a heterogeneous syndrome that causes about 1–2% of all acute hospital hospitalizations. Over the age of 65, it is the most common reason, with up to 20% of patients requiring subsequent rehospitalization for HF decompensation over the next 30 days[2,3]. It is assumed that more than 10% of people in the population over 70 years have some form of HF. According to the most recent European Society of Cardiology (ESC) guidelines from 2016, we divide patients with HF into three subgroups according to left ventricular ejection fraction (LVEF), namely HF with reduced LVEF (HFrEF <40%), HF with mid-range LVEF (HFmEF 40–49%) and with preserved LVEF (HFpEF> 50%) (ref.[4]). HF is a major socio-economic problem, especially in developed countries. In 2012, the cost of treatment worldwide was estimated at $ 108 billion per annum[5].

DM is a major global disease of civilization of the 21st century and it is closely related to HF. It is estimated that about 463 million people in 2019 had some of its types. The trend is growing for both sexes. In 2030 it is estimated to be about 578 million people (10.2% of the world's population) affected with DM worldwide. The basic groups are insulin-dependent type I DM (T1DM), type II DM (T2DM), which accounts for about 90% (associated with insulin resistance) and so-called gestational diabetes (GDM). As many as half of the people with T2DM do not know about their disease. In 2019 alone, the number of deaths from diabetes and its complications reached about 4.2 million people. There are also significant financial costs, which reached $ 760 billion per annum in 2019. It is estimated at up to $ 825 billion per annum in 2030 (ref.[6]).

The relationship between DM and HF development was observed in the 1970s in The Framingham Study. Heart failure was 2 times more common in diabetic men and even 5 times more common in women than in non-diabetic populations[7]. A key finding also for our analysis was that up to 44% of people hospitalized for HF also have DM (ref.[8]).

Apart from DM, the factors contributing to the development of HF are mainly coronary artery disease, arterial hypertension and obesity. However, it is known that the development of HF can occur independently, even in the absence of the above comorbidities, only due to diabetic heart disease – we speak of the so-called diabetic cardio-

myopathy. This unit was first described as early as 1972 (ref.[9,10]).

Although the pharmacological foundations of DM therapy were laid in the early mid-20th century, only new antidiabetics have shown a significant effect on reducing cardiovascular (CV) events, reducing hospitalization and the risk of developing HF, while beneficially affecting overall mortality[11,12].

METHODOLOGY

Study design

Retrospective observational analysis of data of used DM pharmacotherapy in patients with a concommitant diagnosis of HF, reported to the National Register of Paid Health Services (NRHZS) in the Czech Republic during the years 2012–2018.

Patient group

The patient cohort was selected from NRHZS data based on the currently reported DM diagnosis code (E10–E14) or other DM-specific diagnoses and the HF code (I50.x) according to the International Classification of Diseases (ICD-10). An exception are oncological diseases, the incidence of which is assessed on the basis of data from the National Cancer Registry (NOR).

Pharmacotherapy of DM was defined by reporting the drug with the appropriate Anatomical Therapeutic Chemical (ATC) classification code. Patients may have reported multiple different ATC codes during the year, but each patient is counted only once in a given year.

All published data were anonymized before the creation of the research database and complied with the regulations and applicable legislation – the Act on Health Services and the Conditions for their Provision (according to Act 372/2011 of the Collection).

Study aim

Analysis of trends in antidiabetic pharmacotherapy in patients with DM and concomitant HF.

RESULTS

In 2012, a total of 10.52 million people lived in the Czech Republic. 176,496 persons had HF, of which 75,022 (42.5%) had both diagnoses (HF and DM). In 2018, the prevalence of HF increased to 285,745 people out of a total of 10.65 million inhabitants. At the same time, HF and DM had 117,265 people (41%). The development in the prevalence of HF and DM is shown in Table 1.

In the cohort of diabetics with HF in 2018 (n=117,265), there were more men (n=60,855) than women (n=56,410). In contrast, the median age of women was higher (79; 77.9 ± 9.7) than men (73; 72.7 ± 10.2). In the age category over 75 years (in absolute and relative representation) women were more common. The distribution of gender and age is summarized in Fig. 1.

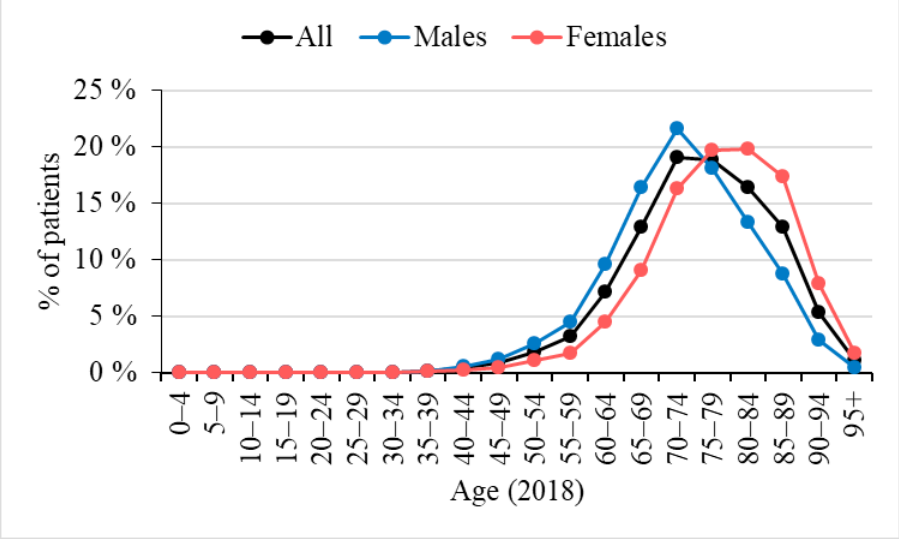

Fig. 1. Distribution of patients with HF and DM by sex and age in 2018.

Table 1. Prevalence and proportion of patients with HF and DM.

Cohort	2012	2013	2014	2015	2016	2017	2018
Prevalence of HF	176 496	202 135	223 808	243 683	256 929	271 907	285 745
Prevalence	75 022	84 514	92 987	100 627	106 114	111 840	117 265
of HF+DM	(42.5%)	(41.8%)	(41.5%)	(41.3%)	(41.3%)	(41.1%)	(41.0%)

In the analyzed patients (n=117,265) with HF and DM (in 2018), the most common comorbidity was arterial hypertension (97.1%; n=113,910), followed by ischemic heart disease (83.2%; n=97,560). Half of the patients had atrial fibrillation (51.5%; n=60,434). A significant part was peripheral arterial disease (34.5%) and renal failure (33.5%). The others are listed in Table 2.

Pharmacotherapy

Between 2012 and 2018, 73.6% of people with DM and concomitant HF were treated with at least one antidiabetic drug. The highest share of the prevalence of HF and DM was reached in the last monitored year (75.7% in 2018; n=88,749). An overview of the following years is summarized in Table 3.

The majority of used therapies were oral diabetics (PAD). In the study period (2012–2018), a total of 56.2% of subjects with antidiabetic therapy (i.e. 43.4% of patients with HF and DM in 2018) used them alone (including subcutaneously administered glucagon-like receptor 1-GLP1-α receptor agonists). Together, PAD (including when combined with insulin) was used by 59.4% of patients with HF and DM in 2018.

Treatment with insulin alone or insulin analogues accounted for (in 2012–2018) 24.1% of antidiabetic therapy (i.e. 16.3 % of the prevalence of HF and DM in 2018). Overall, 32.3% of people diagnosed with HF and DM in 2018 had insulin and insulin analogues (including patients with PAD combination therapy).

Persons with antidiabetic therapy were characterized by a positive trend in the use of PAD (54.9% 2012; 57.3% 2018) and combination therapy (18.7% 2012; 21.1% 2018), on the contrary, a decrease in solo use of insulins and insulin analogues (26.5% 2012; 21.6% in 2018). The development between 2012–2018 is shown in Table 4.

The most used drug in the observed period was classical metformin with an average proportion of 36.9% (34.3% in 2012; 38.3% 2018). Metformin (including its fixed combinations) accounted for 36.5% of antidiabetic treatment in patients with HF and DM in 2012. In the following years, in addition to the introduction of new fixed combinations, this ratio increased (38.1% 2013; 40.3% 2014; 41.9% 2015; 43.3% 2016; 44.1% 2017 and 45.6% 2018).

The main fixed combination with metformin was sitagliptin and vildagliptin (both 1.9% in 2018). The smallest proportion of fixed combinations of metformin was canagliflozin and saxagliptin (both 0.1% in 2018). In the PAD group, a downward trend for sulfonylurea derivatives was evident. Specifically, gliclazide (13.0% 2012; 10.3% in 2018) followed by glimepiride (12.9% 2012; 9.0% 2018). Linagliptin from the group of dipeptidyl peptidase 4 (DDP-4) inhibitors increased significantly (0.7% 2012; 6.8% 2018). Only 0.7% of patients with HF and DM used GLP-1a, of which the most represented in 2018 was liraglutide (0.4%). The number of persons using antidiabetics (excluding insulin and insulin analogues) and their share of the prevalence of HF and DM is given in Table 5.

Table 2. Comorbidities in patients with HF and DM in 2018 (n = 117,265).

Comorbidities	% of all HF + DM	Total
Arterial hypertension	97.1%	113 910
Ischemic heart diseases	83.2%	97 560
Dyslipoproteinemias	58.5%	68 585
Atrial fibrillation	51.5%	60 434
Peripheral artery disease	34.5%	40 508
Chronic obstructive pulmonary disease	34.4%	40 304
Renal failure	33.5%	39 333
Malignant tumors	22.3%	26 162
Stroke	19.4%	22 804
Dementia	12.3%	14 372
Sleep apnoea	3.6%	4 178

Table 3. Antidiabetic therapy in patients with HF and DM.

Cohort	2012	2013	2014	2015	2016	2017	2018
Patients with HF + DM	75 022	84 514	92 987	100 627	106 114	111 840	117 265
Patients with antidiabetics	52 846	60 834	68 197	74 411	795 99	84 147	88 749
% of prevalence HF + DM	70.4%	72.0%	73.3%	73.9%	75.0%	75.2%	75.7%

Table 4. Type of therapy in patients with HF and DM treated with antidiabetic therapy.

	2012		2013		2014		2015		2016		2017		2018	
Cohort	Total	%	Total	%	Total	%	Total	%	Total	%	Total	%	Total	%
Insulin and insulin analogs	13 978	26.4	15 884	26.1	17 018	25.0	17 772	23.9	18 576	23.3	18 954	22.5	19 147	21.6
Peroral antidiabetics	28 994	54.9	33 699	55.4	38 162	56.0	42 029	56.5	45 090	56.6	47 757	56.8	50 878	57.3
Combination therapy	9 874	18.7	11 251	18.5	13 017	19.0	14 610	19.6	15 933	20.1	17 436	20.7	18 724	21.1

Table 5. Number of persons using PAD and their prevalence from HF and DM.

ATC code	Name	2012		2013		2014		2015		2016		2017		2018	
		Number treated	% of prevalence	Number treated	% of prevalence	Number treated	% of prevalence	Number treated	% of prevalence	Number treated	% of prevalence	Number treated	% of prevalence	Number treated	% of prevalence
A10BA02	METFORMIN	25 716	34.3	30 016	35.5	34 414	37.0	37 909	37.7	40 087	37.8	42 180	37.7	44 901	38.3
A10BB01	GLIBENCLAMIDE	1 549	2.1	1 298	1.5	1 049	1.1	901	0.9	721	0.7	537	0.5	447	0.4
A10BB07	GLIPIZIDE	653	0.9	646	0.8	643	0.7	567	0.6	529	0.5	444	0.4	388	0.3
A10BB08	GLIQUIDONE	2 710	3.6	3 004	3.6	3 249	3.5	3 471	3.4	3 569	3.4	3 657	3.3	3 620	3.1
A10BB09	GLICLAZIDE	9 740	13.0	10 677	12.6	11 431	12.3	11 757	11.7	12 111	11.4	12 161	10.9	12 084	10.3
A10BB12	GLIMEPIRIDE	9 661	12.9	10 861	12.9	11 775	12.7	12 057	12.0	11 640	11.0	11 033	9.9	10 585	9.0
A10BD02	METFORMIN AND GLIMENCLAMIDE	297	0.4	270	0.3	306	0.3	286	0.3	257	0.2	232	0.2	206	0.2
A10BD03	METFORMIN AND ROSIGLITAZONE	-	-	-	-	-	-	-	-	-	-	-	-	-	-
A10BD05	METFORMIN AND PIOGLITAZONE	248	0.3	145	0.2	131	0.1	143	0.1	127	0.1	161	0.1	176	0.2
A10BD07	METFORMIN AND SITAGLIPTIN	528	0.7	702	0.8	1 012	1.1	1 386	1.4	1 814	1.7	2 024	1.8	2 262	1.9
A10BD08	METFORMIN AND VILDAGLIPTIN	608	0.8	914	1.1	1 204	1.3	1 529	1.5	1 891	1.8	2 023	1.8	2 172	1.9
A10BD09	PIOGLITAZONE AND ALOGLIPTIN	-	-	-	-	-	-	-	-	-	-	7	0.0	5	0.0
A10BD10	METFORMIN AND SAXAGLIPTIN	-	-	55	0.1	110	0.1	98	0.1	78	0.1	70	0.1	59	0.1
A10BD11	METFORMIN AND LINAGLIPTIN	-	-	127	0.2	272	0.3	429	0.4	514	0.5	695	0.6	898	0.8
A10BD13	METFORMIN AND ALOGLIPTIN	-	-	-	-	-	-	336	0.3	693	0.7	924	0.8	830	0.7
A10BD15	METFORMIN AND DAPAGLIFLOZIN	-	-	-	-	-	-	46	0.0	189	0.2	323	0.3	469	0.4
A10BD16	METFORMIN AND CANAGLIFLOZIN	-	-	-	-	-	-	1	0.0	21	0.0	21	0.0	66	0.1
A10BD20	METFROMIN AND EMPAGLIFLOZIN	-	-	-	-	-	-	-	-	277	0.3	676	0.6	1 139	1.0
A10BF01	ACARBOSE	342	0.5	399	0.5	409	0.4	425	0.4	433	0.4	405	0.4	372	0.3
A10BG02	ROSIGLITAZONE	-	-	-	-	-	-	-	-	-	-	-	-	-	-
A10BG03	PIOGLITAZONE	428	0.6%	505	0.6%	666	0.7	748	0.7	847	0.8	1 251	1.1	1 643	1.4
A10BH01	SITAGLIPTIN	1 042	1.4%	1 029	1.2%	1 356	1.5	1 714	1.7	2 019	1.9	2 203	2.0	2 347	2.0
A10BH02	VILDAGLIPTIN	438	0.6	650	0.8	945	1.0	1 285	1.3	1 533	1.4	1 398	1.3	1 411	1.2
A10BH03	SAXAGLIPTIN	349	0.5	316	0.4	328	0.4	258	0.3	180	0.2	123	0.1	93	0.1
A10BH04	ALOGLIPTIN	-	-	-	-	123	0.1	979	1.0	1 264	1.2	1 441	1.3	1 169	1.0
A10BH05	LINAGLIPTIN	527	0.7	1 198	1.4	2 061	2.2	3 184	3.2	4 550	4.3	6 083	5.4	7 985	6.8
A10BJ01	EXENATIDE (since 2017)	-	-	-	-	-	-	-	-	-	-	104	0.1	68	0.1
A10BJ02	LIRAGLUTIDE (since 2017)	-	-	-	-	-	-	-	-	-	-	451	0.4	442	0.4
A10BJ03	LIXISENATIDE (since 2017)	-	-	-	-	-	-	-	-	-	-	61	0.1	42	0.0
A10BJ05	DULAGLUTIDE	-	-	-	-	-	-	-	-	-	-	15	0.0	279	0.2
A10BK01	DAPAGLIFLOZIN (since 2017)	-	-	-	-	-	-	-	-	-	-	796	0.7	958	0.8
A10BK02	CANAGLIFLOZIN (since 2017)	-	-	-	-	-	-	-	-	-	-	109	0.1	241	0.2
A10BK03	EMPAGLIFLOZIN (since 2017)	-	-	-	-	-	-	-	-	-	-	1 542	1.4	2 146	1.8
A10BX02	REPAGLINIDE	278	0.4	521	0.6	815	0.9	1 029	1.0	1 190	1.1	1 322	1.2	1 632	1.4
A10BX04	EXENATIDE (until 2017)	87	0.1	73	0.1	87	0.1	78	0.1	102	0.1	32	0.0	-	-
A10BX07	LIRAGLUTIDE (until 2017)	280	0.4	339	0.4	388	0.4	461	0.5	534	0.5	140	0.1	-	-
A10BX09	DAPAGLIFLOZIN (until 2017)	-	-	-	-	257	0.3	888	0.9	782	0.7	207	0.2	-	-
A10BX10	LIXISENATIDE (until 2017)	-	-	-	-	91	0.1	107	0.1	87	0.1	26	0.0	-	-
A10BX11	CANAGLIFLOZIN (until 2017)	-	-	-	-	-	-	111	0.1	156	0.1	30	0.0	-	-
A10BX12	EMPAGLIFLOZIN (until 2017)	-	-	-	-	-	-	584	0.6	1 010	1.0	289	0.3	-	-

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Table 6. Number of subjects receiving insulin therapy and prevalence of HF and DM.

ATC code	Name	2012		2013		2014		2015		2016		2017		2018	
		Number treated	% of prevalence	Number treated	% of prevalence	Number treated	% of prevalence	Number treated	% of prevalence	Number treated	% of prevalence	Number treated	% of prevalence	Number treated	% of prevalence
A10AB01	INSULIN (HUMAN) - Fast-acting	10 349	13.8	10 721	12.7	10 700	11.5	10 549	10.5	9 950	9.4	9 148	8.2	8 362	7.1
A10AB04	INSULIN LISPRO	1 839	2.5	2 092	2.5	2 456	2.6	3 156	3.1	3 891	3.7	4 681	4.2	4 950	4.2
A10AB05	INSULIN ASPART	3 402	4.5	4 410	5.2	5 354	5.8	6 196	6.2	6 992	6.6	7 675	6.9	8 788	7.5
A10AB06	INSULINE GLULISINE	813	1.1	1 121	1.3	1 521	1.6	1 862	1.9	2 091	2.0	2 407	2.2	2 607	2.2
A10AC01	INSULIN (HUMAN) - Intermediate-acting	8 532	11.3	8 668	10.3	8 469	9.1	7 974	7.9	6 789	6.4	5 745	5.1	4 845	4.1
A10AD01	INSULIN (HUMAN) - Mixture	4 513	6.0	4 433	5.2	4 080	4.4	3 649	3.6	3 069	2.9	2 669	2.4	2 239	1.9
A10AD04	INSULIN LISPRO	1 549	2.1	2 020	2.4	2 472	2.7	2 880	2.9	2 968	2.8	2 929	2.6	2 933	2.5
A10AD05	INSULIN ASPART (Protamine)	2 071	2.8	2 718	3.2	3 183	3.4	3 551	3.5	3 790	3.6	3 833	3.4	3 636	3.1
A10AE04	INSULIN GLARGINE	4 353	5.8	5 706	6.8	7 322	7.9	9 476	9.4	12 176	11.5	14 905	13.3	17 309	14.8
A10AE05	INSULIN DETEMIR	3 344	4.5	4 284	5.1	5 090	5.5	5 973	5.9	6 597	6.2	6 719	6.0	6 537	5.6
A10AE54	GLARGINE AND LIXISENATIDE	-	-	-	-	-	-	-	-	-	-	-	-	151	0.1
A10AE56	DEGLUDEC AND LIRAGLUTIDE	-	-	-	-	-	-	-	-	54	0.1	736	0.7	1 235	1.1

Of insulin and its analogue, glargine was the most represented (5.8% 2012; 14.8% 2018). A similar positive trend was generated by the fast-acting insulin analogue – aspart (4.5% 2012; 7.5% in 2018). The opposite trend was observed with fast-acting human insulin (13.8% 2012; 7.1% 2018) and intermediate-acting human insulin (11.3% 2012; 4.1% 2018).

Since 2016, we have seen a growing number of users of the fixed combination degludec/liraglutide (0.1% 2016; 1.1% 2018). The number of people using insulin and analogues from the proportion of patients with HF and DM is shown in Table 6.

DISCUSSION

In 2018, there were 117,245 patients with DM and concomitant HF in the Czech Republic, which is 41.0% of diagnosed patients with HF. For comparison, in the Get With the Guidelines-Heart Failure Registry (GWTG-HF), DM was present in 44.0% of hospitalized patients with HF between 2005 and 2015 (overall for all LVEFs) (ref.[8]).

Based on a joint consensus of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), metformin remains the drug of first choice (in general) in patients with T2DM. The advantage of this treatment is easy availability, low cost, minimal risk of hypoglycemia and is not accompanied by weight gain. However, despite modern pharmacotherapy, lifestyle change plays a key role in patients with T2DM (ref.[13]). The recommended treatment for people with T2DM and concomitant HF based on a joint decision of the European Society of Cardiology (ESC) and the European Diabetes Society (EAD) of 2019 includes metfomin and, in this indication, SGLT-2 inhibitors. In contrast, pioglitazone, rosiglitazone and saxagliptin are not recommended for HF and DM (class/level III/B) (ref.[14]).

Metformin reached the highest prevalence in patients with HF and DM in our analysis, which corresponds to other foreign registries. However, compared to the Diabetes Collaborative Registry (DCR), it was less represented (45.6% 2018 vs 57.8%) (ref.[15]). Metformin treatment may be recommended in stable or moderate renal impairment (i.e. eGFR>30 mL/min/1.73 m^2). In the light of new data the previously reported risk of developing lactic acidosis is perceived as minimal[16]. The benefit of metformin in patients with T2DM has been demonstrated in the past by a large United Kingsdom Prospective Diabetes Study (UKPDS), but data from large RCTs on its contribution to reducing the risk of heart failure and/or re-hospitalization in patients with HF and T2DM are still lacking. However, its long-established safety in comparison with other antidiabetic drugs cannot be questioned[17,18].

The role of sodium-glucose co-transporter 2 (SGLT-2) inhibitors is of new and fundamental importance in the therapy of patients with HF and DM. They have been available in the Czech Republic since 2014 and their share is growing every year. In 2018, empagliflozin was the most represented in our country. Overall, SGLT-2 in-

hibitor therapy (without fixed combination with metformin) accounted for 2.8% (vs 2.5% in the DCR registry). Empagliflozin alone reduced HF hospitalization by 35% compared to placebo in the EMPA-REG OUTCOME study in subjects with T2DM. Reduced all-cause death by 32% (ref.[19]). Cannagliflozin also significantly reduced the risk of hospitalization for HF by 32% in the CANVAS study[20]. Another suitable SGLT-2 in the treatment of HF and DM (based on the ESC/EAD recommendation of 2019) is dapagliflozin. In the DECLARE-TIMI study 58, dapagliflozin reduced the risk of hospitalizations for HF (ref.[21]). The key finding was that dapagliflozin (in DAPA-HF) in patients with HFrEF reduced the risk of hospitalization for HF independent of the presence of DM, which opens up completely new possibilities and indications for SGLT-2 inhibitors in the treatment of chronic HF in the future[22]. The second, very significant aspect of SGLT-2 inhibitor treatment is confirmed nephroprotectivity. In our cohort of patients with HF and DM, up to a third of patients had a record of renal failure (33.5% in 2018). A significant renoprotective effect was confirmed by the CREDENCE study (with canagliflozin), which additionally demonstrated the efficacy of canagliflozin up to eGFR 30 mL/min/1.73m^2 (ref.[23]). Significant improvement in renal function while reducing overall mortality in patients with chronic renal insufficiency was also demonstrated by dapagliflozin in the DAPA-CKD study, even independently of the presence of DM (ref.[24]).

A significant (international) decrease in prescription was observed for sulfonylurea derivatives (SU derivatives) (ref.[25]). In our analysis for 2018, they accounted for 23.1% of the prevalence of HF and DM (predominantly represented by glimepiride and gliclazide). Based on the UGDP study with tolbutamide, SU derivatives have been associated with the risk of death from CHD causes since 1960. From today's perspective, the study had significant methodological limitations (randomization method, 20% non-compliance, and others) (ref.[26]). Several large retrospective analyzes confirmed a higher risk of hospitalization for HF in SU derivatives compared to metformin, however, in the CAROLINA study (linagliptin vs glimepiride) glimepiride was non-inferior in CV safety, only a higher proportion of hypoglycemia known[27,28].

Thiazolidinedione drugs, pioglitazone registered in our country, were used by 0.6% of patients with HF and DM in 2012 (1.4% in 2018), despite the known risk of fluid retention and the possibility of worsening of HF. Therefore, neither pioglitazone nor rosiglitazone are recommended in the treatment of DM in patients at risk of developing or pre-existing HF (ref.[14]).

Similar to thiazolidindiones, saxagliptin from the DPP-4 family may worsen HF (SAVOR-TIMI study 53) (ref.[29]). In our analysis, its trend in prescription was declining. However, linagliptin (CARMELINA study) and sitagaliptin (TECOS study) from the same group did not show a significant difference in HF-related outcome compared to placebo[30,31]. They can therefore be recommended in patients with T2DM and HF (ref.[14]). The most significant trend from DPP-4 was recorded by the mentioned linagliptin, both alone and in fixed combination with metformin. Due to its minimal renal clearance, linagliptin is also suitable for patients with advanced renal failure, including dialysis patients, where treatment options for PAD are severely limited. The proportion of DDP-4 in our sample (incl. fixed combinations) was similar to the DCR register (16.5% vs 14.6% DCR in 2018).

Only a small proportion of treatment in patients with HF and DM between 2012 and 2018 were GLP-1, despite having a neutral effect on the risk of hospitalization for HF in their placebo-controlled studies. Subcutaneously administered lixisenatide, liraglutide, semaglutide, dulaglutide and exenatide are therefore also appropriate in patients with HF and DM (ref.[14]). In addition, liraglutide, semaglutide and dulaglutide can be used in advanced renal failure (eGFR> 15 mL/min/1.73m^2). Their small effect on lowering systolic blood pressure (SBP) is also known, which is especially advantageous for patients with arterial hypertension (97.1% in our analysis). Liraglutide and semaglutide therapy reduces the risk of major CV events in individuals with T2DM and at the same time a high CV risk[32].

A significant proportion of patients with HF and DM require insulin therapy to achieve adequate glycemic control. Insulin and analogues are necessary where PAD combination therapy is already insufficient or directly contraindicated. Insulin resistance is known to indirectly contribute to HF progression. The analysis of the TOPCAT study showed a significantly higher risk of hospitalization for heart failure in insulin-treated HFpEF patients than in the PAD group (37.0% vs 22.0% per year) (ref.[33]). However, it is clear that subjects initiating insulin therapy have a higher prevalence of CVD, chronic renal failure, and other significant comorbidities overall compared to the PAD initial therapy group[34]. In our cohort (in 2018), 42.7% of treated patients (i.e. 32.3% of the proportion of patients with HF and DM) used insulin and its analogues (in monotherapy and/or in combination therapy with PAD). For comparison in the DCR register it was 40.9%. The long-acting insulin analogue glargine had the highest proportion, whose CV safety was confirmed by a randomized controlled trial (ORIGIN) (ref.[35]).

Study limitations

A major limitation is the absence of basic knowledge about heart failure, i.e. LVEF, HF etiology, NYHA functional class and natriuretic peptide levels. With regard to the number of patients, the selection bias was reduced, but the accuracy of the entered data and diagnoses cannot be verified. There is a lack of further data on individuals who were reported at the same time as a code for HF and DM, but subsequently did not show any antidiabetic therapy with the ATC code. Patients with HF and T1DM or T2DM were not separately evaluated in the study, whereas a significantly different ratio of antidiabetic therapy (PAD vs insulin) can be expected. There is a lack of data on cured patients over the years. Patients may have been diagnosed with heart failure, for example, in 2012, but already in 2013 they did not have to meet the symptoms and criteria for this diagnosis, although they could still be kept under this diagnosis for the following years. The

patient could have reported several different ATC codes in a given year, therefore, for example, the sum of individual ATC insulins and analogues exceeds the number of patients treated with insulin therapy (each patient is counted only once in a given year). The analysis does not specify and evaluate the cohort of patients who received combination therapy (i.e. insulin and PAD at the same time) in one year, so it is not possible to determine which antidiabetics were most often used in this indication. In 2017, there was a change in the ATC of SGLT-2 inhibitors and GLP-1 antagonists, so one drug is listed in the table twice (until 2017 and from 2017).

CONCLUSION

In the Czech Republic, between 2012 and 2008, there was an evident increase in prevalence of patients with heart failure and concomitant diabetes mellitus, their proportion being similar. In correspondence with other foreign registries, the most widely used antidiabetic drug was metformin. A positive trend was observed in the prescription of DDP-4 and SGLT-2 inhibitors, while there was a significant decrease in patients taking sulfonylureas.

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