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Clinician's guide for empagliflozin use in heart failure

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Abstract

Empagliflozin belongs to the new class of drugs for the treatment of heart failure, sodium-glucose co-transporter type 2 inhibitors. Results of the EMPEROR-Reduced, EMPEROR-Preserved and EMPULSE trials confirmed the clinical benefits of empagliflozin over the whole spectrum of symptomatic heart failure. The present article provides clinicians with practical guidance regarding empagliflozin therapy in HF.

Key words: heart failure, SGLT2 inhibitors, empagliflozin

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Introduction

Empagliflozin is the best studied sodium-glucose co-transporter type 2 (SGLT2) inhibitor in heart failure (HF). The clinical benefits of this drug were initially reported in the EMPAREG-OUTCOME trial [1] which was conducted in patients with diabetes type 2 and documented a reduction of the risk of death, cardiovascular death and hospitalization for HF. Subsequent empagliflozin trials were performed in HF populations, including the EMPEROR-Reduced trial in patients with HF with reduced ejection fraction (HFrEF), the EMPEROR-Preserved trial in patients with HF with preserved ejection fraction (HFpEF), and the EMPULSE trial in patients with acute HF regardless of ejection fraction (EF) [2–4]. All these trials documented **significant clinical benefits of empagliflozin in terms of a reduction of HF events shortly after therapy initiation, along with a nephroprotective effect of the drug.**

The aim of this article is to provide clinicians with practical guidance regarding the use of empagliflozin in HF.

EMPEROR-Reduced trial results

The clinical efficacy of empagliflozin in the treatment of symptomatic chronic HFrEF was documented in the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced), a multicentre, prospective, randomized, placebo-controlled phase III clinical trial which evaluated the efficacy and safety of empagliflozin 10 mg regardless of concomitant diabetes [2]. The study was designed to recruit patients at a high risk of HF events, which was achieved by adequately high threshold N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels depending on EF and/or HF hospitalization during the preceding year. Empagliflozin was added to the standard guideline-based HFrEF therapy, i.e., with an angiotensin-converting enzyme inhibitor (ACEI)/ /angiotensin receptor blocker (ARB) or a dual angiotensin receptor-neprilysin inhibitor (ARNI) and a beta-blocker and/or a mineralocorticoid receptor antagonist (MRA) in stable doses administered for at least a week, along with

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implanted cardiac device therapy, if indicated. The study included 3730 symptomatic New York Heart Association (NYHA) class II–IV patients with chronic HF with EF reduced to ≤ 40%. The EMPEROR-Reduced study was the first empagliflozin trial that recruited patients without diabetes and with impaired renal function, i.e., with the estimated glomerular filtration rate (eGFR) 20 mL/min/1.73 m^2 and more.

The study inclusion and exclusion criteria are shown in Table 1.

The patient population in the EMPEROR-Reduced study received optimal HF care, with 88% of patients treated with ACEI/ARB/ARNI (including 18% receiving ARNI), 95% treated with a beta-blocker, and 71% treated with MRA. In addition, 31% of patients had an implantable cardioverter-defibrillator (ICD), and 12% had a cardiac resynchronization therapy (CRT) device implanted.

During the median follow-up of 16 months, **empagliflozin treatment compared to placebo was associated with a 25% reduction in the risk of the primary endpoint of cardiovascular death and first hospitalization due to HF (p < 0.001)** (Table 2). The primary endpoint occurred in 361 of 1863 patients (19.4%) receiving empagliflozin and 462 of 1867 patients (24.7%) receiving placebo [hazard ratio (HR) 0.75; 95% confidence interval (CI): 0.65–0.86; p < 0.0001], and the number needed to treat (NNT) was 19. Regarding the individual components of the primary endpoint, statistical significance was reached for the reduction of hospitalizations due to HF (Table 2). The benefits from empagliflozin therapy for the primary endpoint

Table 1. Main inclusion and exclusion criteria in the EMPEROR-Reduced trial [2]

Inclusion criteria	Exclusion criteria
Age > 18 years	Myocardial infarction, coronary artery bypass grafting or other major cardiovascular procedure, stroke or TIA within ≤ 90 days
Chronic heart failure (NYHA class II–IV) with reduced ejection fraction (≤ 40%) and elevated NT-proBNP level (depending on ejection fraction, cardiac rhythm, and the history of hospitalization for heart failure)	Cardiac transplant recipient or on the waiting list
Optimal treatment of heart failure	Acute heart failure
	Systolic blood pressure > 180 mm Hg
	Symptomatic hypotension or systolic blood pressure < 100 mm Hg
	eGFR < 20 mL/min/1.73m^2 or dialysis therapy
	History of ketoacidosis

eGFR — estimated glomerular filtration rate; NT-proBNP — N-terminal pro-B-type natriuretic peptide; NYHA — New York Heart Association; TIA — transient ischemic attack

Table 2. Primary and secondary endpoints in the EMPEROR-Reduced trial [2]

Outcome	Empagliflozin n = 1863 n (%)	Placebo n = 1867 n (%)	Hazard ratio (95% CI)	p
Combined primary endpoint	361 (19.4)	462 (24.7)	0.75 (0.65–0.86)	< 0.001
Cardiovascular death	187 (10.0)	202 (10.8)	0.92 (0.75–1.12)	–
Hospitalization for HF	246 (13.2)	342 (18.3)	0.69 (0.59–0.81)	< 0.001
Secondary endpoints				
All hospitalizations for HF (initial and recurrent)	388	553	0.70 (0.58–0.85)	< 0.001
Annual eGFR change (eGFR slope)	–0.55 ± 0.23	–2.28 ± 0.23	1.73 (1.1–2.37)	< 0.001
Other prespecified outcomes				
Combined renal endpoint	30 (1.6)	58 (3.1)	0.5 (0.32–0.77)	
All hospitalizations	1364	1570	0.85 (0.75–0.95)	
All-cause death	249 (13.4)	266 (14.2)	0.92 (0.77–1.10)	
KCCQ[1] change at 52 weeks	5.8 ± 0.4	4.1 ± 0.4	1.7 (0.5–3.0)	
Diabetes *de novo* in patients with prediabetes	71/632 (11.2)	80/636 (12.6)	0.86 (0.62–1.19)	

[1]Kansas City Cardiomyopathy Questionnaire (KCCQ) score from 0 to 100, with higher scores indicating less severe HF symptoms; CI — confidence interval; eGFR — estimated glomerular filtration rate; HF — heart failure

were independent of baseline haemoglobin A1c level [5]. The study also documented a beneficial effect of empagliflozin on the risk of secondary endpoints (Table 2) which included [2]:

- total (first and recurrent) hospitalizations due to HF; and
- renal function impairment as determined by annual eGFR decline (eGFR slope);

and in the remaining analyses that included:

- all-cause hospitalizations;
- all-cause mortality;
- quality of life improvement as evaluated by the Kansas City Cardiomyopathy Questionnaire (KCCQ) questionnaire at 52 weeks compared to baseline;
- combined renal end-point, defined as chronic dialysis therapy or kidney transplantation or persisting eGFR reduction by ≥ 40%, or permanent eGFR reduction to < 15 mL/min/1.73 m^2 in patients with eGFR ≥ 30 mL/min/1.73 m^2 or to < 10 mL/min/1.73 m^2 in patients with eGFR < 30 mL/min/1.73 m^2;
- incident diabetes in patients with prediabetes.

Detailed results of the EMPEROR-Reduced trial are showed in Table 2.

The benefits from empagliflozin therapy in terms of the primary endpoint risk reduction were independent of concomitant presence of diabetes type 2, left ventricular EF (LVEF), aetiology of HF, standard HF care in terms of drug classes (including ARNI) and doses used [6], and device therapy (ICD/CRT) used, which indicates a complementary effect of empagliflozin in addition to other HFrEF therapies, and the possibility of initiating this treatment at any stage of HF therapy. The benefits were also independent of the severity of clinical symptoms as measured by the NYHA class but were higher in lower NYHA class (i.e., class II) [2]. Thus, initiation of empagliflozin treatment should occur early and not be delayed until more severe HF symptoms develop.

A beneficial effect of 58% reduction of the risk of all-cause death, hospitalization due to HF, or an urgent visit due to HF, including an emergency department visit with intravenous drug administration, was documented as early as at 12 days of therapy (HR 0.42; 95% CI: 0.19–0.92; p = 0.029) [7]. Empagliflozin reduced the risk of hospitalization with the need for admission to an intensive care unit (HR 0.67; 95% CI: 0.5–0.9; p = 0.008), and hospitalization requiring administration of vasopressors or inotropic agents, circulatory support, or surgical intervention (HR 0.64; 95% CI: 0.47–0.87; p = 0.005) [7]. It was also found that patients treated with empagliflozin less frequently required diuretic treatment intensification (HR 0.67; 95% CI: 0.58–0.78; p < 0.0001) and more frequently experienced clinical improvement (and less frequently clinical worsening) as evaluated by the NYHA functional class (20–40% higher likelihood of clinical improvement and 20–40% lower risk of clinical worsening as evaluated by the NYHA class) [7]. Clinical improvement as evaluated by the NYHA functional class was significant as early as at 28 days after therapy initiation and persisted during further follow-up (p < 0.05). Diuretic doses were more frequently reduced in the empagliflozin group (n = 334 with empagliflozin vs. n = 291 with placebo) [7].

In the EMPEROR-Reduced study population, empagliflozin rapidly (since 4 weeks of treatment) increased haematocrit and haemoglobin level and reduced the rate of incident anaemia (22.6% in the placebo group vs. 12.3% in the empagliflozin group; HR 0.49; 95% CI: 0.41–0.59; p < 0.001) [8]. The clinical effect of reduction of the risk of primary endpoint, all hospitalizations due to HF, and combined renal endpoint by empagliflozin was not modified by the baseline anaemia status (p for interaction > 0.1) [8].

The benefits of empagliflozin were similar in all categories of baseline systolic blood pressure for both HF events and the nephroprotective effect [9].

In 2021, based on the EMPEROR-Reduced study results, the European Medicines Agency and the Food and Drug Administration approved empagliflozin for the treatment of patients with symptomatic chronic HFrEF. **After dapagliflozin, Jardiance™ is the second SGLT2 inhibitor approved for the treatment of HFrEF.**

EMPEROR-Preserved trial results

The clinical efficacy of empagliflozin in the treatment of symptomatic chronic HFpEF was documented in the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-Preserved), a multicentre, prospective, randomized, placebo-controlled phase III clinical trial which evaluated the efficacy and safety of empagliflozin 10 mg regardless of concomitant diabetes [3].

The trial was performed in 5988 symptomatic NYHA class II–IV patients with chronic HF with preserved EF (> 40%). Similarly to the EMPEROR-Reduced study, this trial also included patients with impaired renal function (eGFR ≥ 20 mL/min/1.73 m^2).

The inclusion and exclusion criteria are shown in Table 3.

During the median follow-up of 26.2 months, **empagliflozin treatment compared to placebo was associated with a 21% reduction in the risk of the primary endpoint of cardiovascular death and first hospitalization due to HF (p < 0.001)** (Table 4), with NNT of 31 [3]. Regarding the individual components of the primary endpoint, statistical significance was reached for the reduction of hospitalizations due to HF (Table 4). The study also documented a beneficial effect of empagliflozin on the risk of secondary endpoints (Table 4) which included [3]:

- total (first and recurrent) hospitalizations due to HF; and
- renal function impairment as determined by annual eGFR decline;

Table 3. Selected inclusion and exclusion criteria in the EMPEROR-Preserved trial [3]

Inclusion criteria	Exclusion criteria
Age > 18 years	Myocardial infarction, coronary artery bypass grafting or other major cardiovascular procedure, stroke or TIA within ≤ 90 days
Chronic heart failure (NYHA class II–IV)	Cardiac transplant recipient or on the waiting list
LVEF > 40%	Acute heart failure
NT-proBNP level: • > 300 pg/mL in patients without AF • > 600 pg/mL in patients with AF	Symptomatic hypotension or systolic blood pressure < 100 mm Hg eGFR < 20 mL/min/1.73m^2 or dialysis therapy

AF — atrial fibrillation; eGFR — estimated glomerular filtration rate; LVEF — left ventricular ejection fraction; NT-proBNP — N-terminal pro-B-type natriuretic peptide; NYHA — New York Heart Association; TIA — transient ischemic attack

Table 4. Results of the EMPEROR-Preserved trial [3]

Outcome	Empagliflozin n = 2997	Placebo n = 2991	Hazard ratio (95% CI)	p
Combined primary endpoint	415 (13.8%)	511 (17.1%)	0.79 (0.69–0.90)	< 0.001
Hospitalization for heart failure	259 (8.6%)	352 (11.8%)	0.71 (0.60–0.83)	< 0.001
Cardiovascular death	219 (7.3%)	244 (8.2%)	0.91 (0.76–1.09)	
Secondary endpoints				
All hospitalizations for heart failure	407	541	0.73 (0.61–0.88)	< 0.001
Mean annual eGFR decline [mL/min/1.73m^2]	–1.25 ± 0.11	–2.62 ± 0.11	1.36 (0.87–1.15)	< 0.001
Other prespecified outcomes				
KCCQ1 change at 52 weeks	4.51 ± 0.31	3.18 ± 0.31	1.32 (0.45–2.19)	
All hospitalizations for any cause	2566	2769	0.93 (0.85–1.01)	
Combined renal endpoint	108 (3.6%)	112 (3.7%)	0.95 (0.73–1.24)	
Diabetes de novo in patients with prediabetes	120 (12.0)	137 (14.0)	0.84 (0.65–1.07)	
All-cause death	422 (14.1%)	427 (14.3%)	1.00 (0.87–1.15)	

[1]Kansas City Cardiomyopathy Questionnaire (KCCQ) score from 0 to 100, with higher scores indicating less severe HF symptoms; CI — confidence interval; eGFR — estimated glomerular filtration rate; HF — heart failure

and in the remaining analyses that included:

- quality of life improvement as evaluated by the KCCQ questionnaire at 52 weeks compared to baseline;
- all-cause hospitalizations;
- all-cause mortality;
- combined renal end-point, defined as chronic dialysis therapy or kidney transplantation or persisting eGFR reduction by ≥ 40%, or permanent eGFR reduction to < 15 mL/min/1.73 m^2 in patients with eGFR ≥ 30 mL/min/1.73 m^2 or to < 10 mL/min/1.73 m^2 in patients with eGFR < 30 mL/min/1.73 m^2;
- incident diabetes in patients with prediabetes.

Detailed results of the EMPEROR-Preserved trial are showed in Table 4.

The benefits from empagliflozin therapy in terms of the primary endpoint risk reduction were independent of concomitant presence of diabetes type 2, chronic kidney disease, and atrial fibrillation, LVEF, gender, age, concomitant drug treatment (including with MRA), and the severity of clinical symptoms as measured by the NYHA class and previous hospitalization due to HF (but were higher in lower NYHA class, i.e., class II, and with the history of hospitalization due to HF) [3]. Thus, initiation of empagliflozin treatment should occur early, also after a hospitalization, and not be delayed until more severe HF symptoms develop.

In the EMPEROR-Preserved trial, **a beneficial effect in terms of the reduction of the risk of the primary endpoint was documented in the empagliflozin group as early as at 18 days after therapy initiation (HR at 18 days 0.41; 95% CI: 0.17–0.99) and persisted during further follow-up** [10]. Similarly, a significant and persisting improvement was noted early for all the evaluated quality of life domains and the clinical symptoms as evaluated by the NYHA class, starting from 3 months and 4 weeks, respectively [10]. In addition, the empagliflozin group showed a higher rate of quality of life improvement by at least 5 points in the KCCQ score (OR 1.23; 95% CI: 1.1–1.37) and a lower risk of worsening by at least 5 points in the KCCQ score (OR 0.85; 95% CI: 0.75–0.97) at 12 weeks [11].

Table 5. Selected inclusion and exclusion criteria in the EMPULSE trial [4]

Inclusion criteria	Exclusion criteria
Current hospitalization for acute heart failure regardless of LVEF	Current hospitalization for acute heart failure due to pulmonary embolism, cardiovascular event, acute myocardial infarction
Systolic blood pressure > 100 mm Hg without symptoms of hypotension within last 6 hours	Myocardial infarction, coronary artery bypass grafting or other major cardiovascular procedure, stroke or TIA within ≤ 90 days
Stable intravenous diuretic dose within last 6 hours	Diabetes type 1
NT-proBNP level ≥ 1600 pg/mL or BNP level ≥ 400 pg/mL during hospitalization or within 72 hours before admission	eGFR < 20 mL/min/1.73m^2 or dialysis therapy
No intravenous vasodilator therapy within last 6 hours	
No intravenous inotropic therapy within last 24 hours	

BNP — B-type natriuretic peptide; eGFR — estimated glomerular filtration rate; LVEF — left ventricular ejection fraction; NT-proBNP — N-terminal pro-B-type natriuretic peptide; TIA — transient ischemic attack

An early beneficial effect of empagliflozin was also documented for the extended primary endpoint that also included an urgent visit due to HF, including an emergency department visit with intravenous drug administration, noted as early as at 18 days of therapy (HR 0.77; 95% CI: 0.67–0.87; p < 0.001) [12]. **Empagliflozin reduced the risk of intensive care unit admission due to HF (HR 0.71; 95% CI: 0.52–0.96; p = 0.028), and the risk of all hospitalizations requiring administration of vasopressors or inotropic agents, (HR 0.73; 95% CI: 0.55–0.97; p = 0.033). Compared to the placebo group, patients treated with empagliflozin less frequently required outpatient intensification of diuretic therapy (HR 0.76; 95% CI: 0.67–0.86; p < 0.001) and were 20% to 50% more likely to have less severe HF symptoms (as indicated by lower NYHA class) starting at 12 weeks of therapy, with the effect persisting for up to 2 years [12].** The beneficial effect in terms of a lower risk of hospitalization due to HF was similar in patients with EF > 40% to < 50% and those with EF 50% to 60% [12].

The EMPEROR-Preserved study is the first trial in HFpEF that showed the efficacy and safety of empagliflozin which is currently the only drug known to improve clinical outcomes in the population with HFpEF.

In the combined analysis of the EMPEROR-Reduced and EMPEROR-Preserved trials [13], encompassing the total of 9718 patients, **empagliflozin was shown to bring similar clinical benefits, resulting in about 30% reduction of the risk of the primary endpoint, in a wide range of EF, from <25% to <65%. Similar results were obtained for the other evaluated endpoints, including KCCQ variables.** No effect of gender on these results was noted.

EMPULSE trial results

Empagliflozin also improves outcomes in patients with acute HF. In the multicentre, randomised, double-blind, 90-day superiority trial to evaluate the effect on clinical benefit, safety and tolerability of once daily oral EMPagliflozin 10 mg compared to placebo, initiated in patients hospitalised for acUte heart faiLure (*de novo* or decompensated chronic HF) who have been StabilisEd (EMPULSE), empagliflozin was compared to placebo in patients hospitalized due to acute HF (*de novo* or decompensated chronic HF) regardless of EF [4]. In this trial, 530 patients were randomized to empagliflozin 10 mg or placebo for 90 days. Empagliflozin therapy was initiated during the hospital stay, after clinical stability is achieved, most commonly at 3 days. The main inclusion and exclusion criteria are shown in Table 5. **Patients receiving empagliflozin were 36% more likely (stratified win ratio 1.36; 95% CI: 1.09–1.68; p = 0.0054) to experience a clinical benefit, defined as reduced cardiovascular mortality risk, lower rate of hospitalizations due to HF, or improved quality of life, compared to those receiving placebo (benefit in 53.9% in the empagliflozin group vs. 39.7% in the placebo group; p = 0.0054)** [4]. The benefit was independent of EF in both HFrEF and HFpEF, duration of HF (HF *de novo* vs. exacerbated chronic HF), and concomitant diabetes. Mortality was 4.2% in the empagliflozin group vs. 8.3% in the placebo group, a HF event occurred in 10.6% vs. 14.7% of patients, respectively, the change in the KCCQ-Total Symptom Score (TSS) over 90 days of treatment a mean of 36.19 points vs. 31.73 points, respectively, with a greater absolute benefit for empagliflozin [mean difference by 4.45 points (95% CI: 0.32–8.59)] and there was a greater reduction in NT-proBNP for empagliflozin at day 30 than in the placebo group (adjusted geometric mean ratio 0.90; 95% CI: 0.82–0.98).

The results for the secondary endpoints are shown in Table 6. Empagliflozin is safe in patients with acute HF, and the rates of hypotension and ketoacidosis were not increased, acute kidney injury occurred in 7.7% for empagliflozin vs. 12.1% for placebo, respectively. **The EMPULSE trial is the first study that showed the efficacy and safety of a SGLT2 inhibitor in patients hospitalized for acute HF.**

Table 6. Secondary endpoints in the EMPULSE trial [4]

	Empagliflozin n = 265	Placebo n = 265	Comparison (95% CI)
Cardiovascular death or hospitalization for HF by the study end, n (%) [events per 100 patient-years]	34 (12.8) [55.01]	48 (18.1) [78.81]	HR: 0.69 (0.45; 1.08)
KCCQ-TSS[1] improvement by ≥ 10 points at 90 days, n (%)	220.1 (83.1)	202.1 (76.3)	OR: 1.522 (0.927; 2.501)
KCCQ-TSS[1] change at 90 days compared to baseline, adjusted mean (95% CI)	36.19 (33.28; 39.09)	31.73 (28.80; 34.67)	Difference: 4.45 (0.32; 8.59)
Diuretic response* (excluding patients who did not receive diuretics for more than 1 day)			
At 15 days, median (IQR)	−1.70 (−5.36; 0.00)	−0.86 (−3.66; 0.93)	NA
At 30 days, median (IQR)	−1.93 (−5.60; 0.84)	−0.58 (−4.59; 1.60)	NA
AUC change compared to baseline NT-proBNP level at 30 days, adjusted geometric mean (95% CI)	24.07 (22.61; 25.62)	26.77 (25.15; 28.48)	Ratio: 0.90 (0.82; 0.98)

[1]Kansas City Cardiomyopathy Questionnaire-Total Symptom Score (KCCQ-TSS) from 0 to 100, with higher scores indicating less severe HF symptoms; *Weight loss/daily dose of diuretic; AUC — area under curve; CI — confidence interval; HF — heart failure; IQR — interquartile range; NA — not applicable; NT-proBNP — N-terminal pro-B-type natriuretic peptide

In whom empagliflozin should be initiated in HF?

According to the current summary of product characteristics (SPC), **empagliflozin is indicated in adult individuals with symptomatic chronic HF [14].**

In patients with HF, empagliflozin dose does not need to be modified when renal function is impaired [14]. Initiating and continuing empagliflozin therapy is possible with eGFR ≥ 20 mL/min/1.73m^2 or creatinine clearance ≥ 20 mL/min. However, the experience with empagliflozin for the treatment of HF in patients with severe renal dysfunction (eGFR < 20 mL/min/1.73m^2) and patients undergoing dialysis therapy is limited.

Similarly, there is no need for drug dose adjustment in patients with mild to moderate hepatic dysfunction [14]. The experience with empagliflozin in patients with severe hepatic dysfunction is limited.

How to initiate empagliflozin therapy?

Empagliflozin may be added to any HF therapy [6], including both drug and device therapy, and regardless of the other drug doses used. According to the SPC, the recommended dose of empagliflozin in HF is 10 mg once daily. Empagliflozin therapy in patients with HFrEF should be initiated early, optimally at the diagnosis or before hospital discharge or at a follow-up outpatient visit soon after the patient is discharged following HFrEF exacerbation [12]. The drug may be taken at any time of the day, regardless of meals (with a meal or between meals).

The drug may be used regardless of the diabetes status and its treatment. However, if the patient is treated with a sulphonylurea, metformin, and/or insulin, reduction of their doses should be considered due to a risk of hypoglycaemia [14]. It should also be noted that with eGFR < 45 mL/min/1.73 m^2, the effectiveness of SGLT2 inhibitors may be suboptimal and use of additional antidiabetic drugs should be considered to improve blood glucose control [14].

Safety of empagliflozin therapy

Empagliflozin has been used in the clinical practice for the treatment of diabetes type 2 for 8 years. In 2021, more than 6.6 million patients were treated with empagliflozin (data based on IQVIA Global Volume Data [days of therapy] and assuming a [conservative] compliance rate of 100%) (Iqvia 04.22). Clinical trial and real world evidence collected over several years indicate that **empagliflozin is a safe drug. The overall safety profile of empagliflozin has been consistent in all studies performed. Adverse events (AEs), serious AEs, and AEs leading to treatment discontinuation are rare, occurring at rates similar to those in the placebo group** [2–4].

The most commonly noted AEs were dehydration and renal events [2–4], while genital and urinary infections were a marginal problem.

According to the SPC, there is no need to withdraw empagliflozin treatment in case of mild to moderate genitourinary infections. Topical antifungal therapy or administration of a single dose of antifungal drug is recommended.

Severe hypoglycaemic episodes were infrequent and occurred **mostly in patients with diabetes type 2** [2–4].

Of note in the context of HFrEF therapy, empagliflozin may reduce the risk of moderate/severe hyperkalaemia in patients treated with MRA and ACEI/ARNI [6].

Practical guidance

During empagliflozin therapy in the EMPEROR-Reduced and EMPEROR-Preserved trials, the following changes were observed [2, 3]:

- systolic blood pressure fall (on average by 2.4 mm Hg and 1.8 mm Hg, respectively);
- NT-proBNP level reduction (on average by 244 pg/mL and 29 pg/mL, respectively);
- body weight reduction (on average by 0.73 kg and 1.39 kg, respectively);
- HbA1c level reduction in patients with diabetes (on average by 0.28% and 0.16%, respectively); and
- increase in haematocrit (on average by 1.98% and 1.94%, respectively).

During SGLT2 inhibitor therapy, patients should be informed about the presence of glucose in urine, resulting in positive urinalysis for glucose, which is related to the drug's mechanism of action. Urinary glucose excretion may be associated with an increased risk of genital infections, and less frequently urinary tract infections. Temporary interruption of empagliflozin therapy should be considered during pyelonephritis or a complicated urinary tract infection. During empagliflozin therapy, the patients should be advised to pay due attention to genital hygiene.

During the first 2 weeks of empagliflozin therapy, a transient decrease in eGFR may be expected. This is related to afferent arteriole constriction due to tubuloglomerular feedback stimulated by an increased sodium influx to the macula densa. During further follow-up in the EMPEROR--Reduced and EMPEROR-Preserved trials, the rate of eGFR decrease in the empagliflozin group was lower than in the placebo group, reflecting the **nephroprotective effect of the drug**.

Renal function should be evaluated prior to initiating empagliflozin therapy and thereafter monitored at least annually (serum creatinine level and eGFR). If eGFR is reduced to < 20 mL/min/1.73 m^2 during empagliflozin therapy, it is recommended to evaluate volume status, blood pressure and other reversible risk factors for renal function worsening (e.g., concomitant medications, contrast agent use for imaging), correct any identified predisposing factors, and reevaluate eGFR with an individual decision whether to continue empagliflozin in a given clinical situation.

Due to to a possible risk of hypovolaemia and hypotension during empagliflozin therapy, particularly in the elderly individuals and those with a history of hypotension, patients should be informed about the need to maintain adequate hydration, and possibly adjust the previous doses of diuretics, other antihypertensive drugs, and other medications used for the treatment of HF.

Diabetic ketoacidosis

Diabetic ketoacidosis during SGLT2 inhibitor therapy does not develop in non-diabetic patients. In those with diabetes type 2, it occurs rarely but may be life-threatening. Diabetic ketoacidosis is more frequent during insulin therapy, with suboptimal blood glucose control, even with moderately increased blood glucose levels, and during the first 2 months of therapy.

It is recommended to assess the risk of diabetic ketoacidosis which is increased in the following situations:

- conditions leading to hypoalimentation or severe dehydration;
- sudden fall in insulin level or increased insulin requirement due to acute illness, surgery or alcohol abuse;
- low beta cell functional reserve, e.g. in patients with diabetes type 2 and low peptide C level or latent autoimmune diabetes in adults and patients with a history of pancreatitis.

The patients should be informed about the symptoms of ketoacidosis (abdominal pain, nausea, vomiting, anorexia, thirst, confusion, rapid deep breathing with sweet, "fruity" breath odor, atypical fatigue and somnolescence) and the need to contact a physician should these symptoms occur. The diagnosis of diabetic ketoacidosis requires interruption of SGLT2 inhibitor therapy. Reinitiation of SGLT2 inhibitor therapy is possible after stabilization of the clinical status and reduction of blood ketone level, when other obvious causes of diabetic ketoacidosis have been identified and addressed.

No cases of diabetic ketoacidosis were reported in the EMPEROR-Reduced trial, and they were rare in both treatment groups in the EMPEROR-Preserved trial (0.1% vs. 0.2% in the placebo group).

Precautions

Empagliflozin should be used with caution in the following situations:

- severe renal dysfunction;
- history of diabetic ketoacidosis;
- recurrent genitourinary infections;

Treatment should be temporarily withdrawn in patients with diabetes type 2 hospitalized for severe acute illness or major surgery (aiming for a 3-day treatment interruption before the procedure).

Excessive alcohol intake and use of ketogenic diets are contraindicated during empagliflozin therapy.

Contraindications to empagliflozin

As per SPC [14], use of Jardiance™ is contraindicated in patients with hypersensitivity to the active ingredient or any other medication excipient. The drug should not be used in patients with rarely occurring hereditary galactose intolerance, total lactase deficiency or glucose-galactose malabsorption, as the tablets contain lactose. Other contraindications to empagliflozin are pregnancy and diabetes type 1.

Summary

Empagliflozin is the first SGLT2 inhibitor with clinical benefits documented over the whole HF spectrum regardless of EF and in all populations of HF patients, both outpatients and those hospitalized for exacerbated HF and HF *de novo*. Empagliflozin is a well-tolerated, safe, and easy to use drug. It acts rapidly, modifies the clinical course of HF, improves quality of life regardless of concomitant presence of diabetes type 2, and exerts a nephroprotective effect.

Conflict of interests

Lectures and clinical trials for Boehringer Ingelheim.

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