European Heart Journal Supplements (2023) **25** (Supplement D), D274–D280
The Heart of the Matter
https://doi.org/10.1093/eurheartjsupp/suad107

ESC European Society of Cardiology

Italian Association of Hospital Cardiologists practical guidance for sodium–glucose cotransporter 2 inhibitors use in patients with heart failure

Stefania Angela Di Fusco[1]*, Antonella Spinelli[1], Stefano Aquilani[1], Nunzia Borrelli[2], Gianmarco Iannopollo[3], Michele Massimo Gulizia[4], Domenico Gabrielli[5,6], Fabrizio Oliva[7], and Furio Colivicchi[1]

[1]U.O.C. Cardiologia Clinica e Riabilitativa, Presidio Ospedaliero San Filippo Neri—ASL Roma 1, PO San Filippo Neri, via Martinotti 20, Rome 00135, Italy; [2]Unità di Malattie Cardiache Congenite dell'Adulto, AORN dei Colli—Ospedale Monaldi, Via Leonardo Bianchi, 80131 Naples, Italy; [3]UOC Cardiologia, Ospedale Maggiore Carlo Alberto Pizzardi, Largo Bartolo Nigrisoli 2, 40133 Bologna, Italy; [4]U.O.C. Cardiologia, Ospedale Garibaldi-Nesima, Azienda di Rilievo Nazionale e Alta Specializzazione 'Garibaldi', Via Palermo 636, 95122 Catania, Italy; [5]U.O.C. Cardiologia, Dipartimento Cardio-Toraco-Vascolare, Azienda Ospedaliera San Camillo Forlanini, Circonvallazione Gianicolense 87, 00152 Rome, Italy; [6]Fondazione per il Tuo cuore—Heart Care Foundation, VIA Alfonso La Marmora 36 - 50121 Florence, Italy; and [7]Unità di Cure Intensive Cardiologiche, Cardiologia 1-Emodinamica, Dipartimento Cardiotoracovascolare 'A. De Gasperis', ASST Grande Ospedale Metropolitano Niguarda, Piazza Ospedale Maggiore, 3 - 20162 Milan, Italy

KEYWORDS
Heart failure;
Sodium–glucose cotransporter 2 inhibitors;
Pharmacotherapy;
Prognosis

Sodium–glucose cotransporter 2 inhibitors (SGLT2-is) have recently been included among the first-line drugs for the treatment of heart failure with reduced ejection fraction. International guidelines recommend SGLT2-i use in association with neuro-hormonal modulators (renin–angiotensin blockers, beta blockers, and aldosterone antagonists). Although SGLT2-is are well tolerated, it is important to know potential side effects and conditions that may lead to an increased risk of adverse events in order to maximize clinical benefits. The aim of this Italian Association of Hospital Cardiologists document is to briefly report clinical evidence that supports SGLT2-i use in patients with heart failure and provide practical indications for clinical implementation.

Introduction

Heart failure is a clinical syndrome associated with an increased risk of adverse events such as hospitalization and death. Heart failure is a pandemic with a worldwide prevalence of more than 64 million cases according to recent epidemiological data.[1] Pharmacological therapy aimed at improving quality of life, functional capacity, and prognosis represents the basis of heart failure treatment and must be implemented before considering implantable devices.[2] Over the last decade, the impact of novel therapeutic approaches on the prognosis of patients with heart failure has been evaluated by different studies with a consequent increase in the number of drugs recommended by international guidelines for the treatment of heart failure.

The latest European Society of Cardiology (ESC)[2] and American College of Cardiology/American Heart Association[3] guidelines recommend sodium–glucose cotransporter 2 inhibitors (SGLT2-is) as first-line drugs for the treatment of heart failure with reduced ejection fraction (HFrEF) alongside beta blockers, renin–angiotensin system inhibitors (RASi)/sacubitril antagonists, and mineralocorticoid receptor antagonists. Sodium–glucose cotransporter 2 inhibitor, also called gliflozins, are a class

*Corresponding author. Tel: +0039 3491500982, Fax: +0039 0633062294, Email: doctstefania@hotmail.com

© The Author(s) 2023. Published by Oxford University Press on behalf of European Society of Cardiology.
This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (https://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

of drugs initially developed for the treatment of diabetes. Recent clinical studies aimed at evaluating SGLT2-i (dapagliflozin and empagliflozin) cardiovascular (CV) safety in diabetic patients demonstrated a clear safety benefit and a better prognosis in patients with heart failure by reducing CV events and mortality.[4,5] Accordingly, randomized clinical trials (RCTs) have been conducted to evaluate the effect of SGLT2-i in patients with heart failure regardless of the presence of diabetes mellitus.[6,7] These studies confirmed and strengthened previous evidence, and as a result, empagliflozin and dapagliflozin have been added to the therapeutic armamentarium for the treatment of heart failure.

This National Association of Hospital Cardiologists (ANMCO) document aims to summarize the clinical evidence of dapagliflozin and empagliflozin efficacy in the context of heart failure, with insights into its renal benefits. Furthermore, its objective is to guide physicians in their clinical practice use, also with regard to national regulatory authority indications.

Mechanism of action and clinical evidence

The clinical evidence in favour of SGLT2-i use in patients with heart failure are robust; however, the biological mechanisms underlying the clinical benefit have not yet been fully elucidated. Glycosuria and natriuresis[8] are well-known effects of these drugs that cannot explain the benefit observed in patients with heart failure and normoglycaemia. Therefore, further effects have been hypothesized to include an improvement in endothelial function and remodulation of the sympathetic nervous system activity,[9] increased erythropoietin production,[10] and a favourable action on ionic homeostasis at the myocardiocyte level.[11] In particular, it is not well established whether the haemodynamic effect mediated by the action that SGLT2-i exerts on the renal tubule is the main mechanism underlying the clinical benefit observed in patients with heart failure or whether this effect is negligible.[12]

Two large RCTs, Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF)[6] and Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced),[7] have supported the use of SGLT2-i in HFrEF, where a 25–26% reduction in the primary composite endpoint of heart failure hospitalization and cardiovascular death was demonstrated. Specifically, the use of recommended medical therapy for HFrEF was optimal (~95% of patients treated with beta blockers and ~71% treated with mineralocorticoid receptor antagonists in both studies; 83% treated with RASi in DAPA-HF and 70% in EMPEROR-Reduced), and in the subgroup analysis, the efficacy of SGLT2-i treatment was independent of concomitant drug therapy and diabetes mellitus. Even patients treated with RASi, beta blockers, and mineralocorticoid receptor antagonists at less than half of the recommended target doses[6] had an improved prognosis. On the basis of the benefit observed in patients with HFrEF treated with SGLT2-i and in light of the lack of therapies able to improve prognosis in patients with heart failure and mildly reduced or preserved left ventricular ejection, these drugs have also been tested in these settings. The Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-Preserved)[13] and the Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER)[14] demonstrated that both empagliflozin and dapagliflozin reduced the combined endpoint of heart failure hospitalization and cardiovascular mortality (−21% and −18%, respectively), mainly due to the reduction in heart failure hospitalization, with efficacy found in all ejection fraction subgroups. *Table 1* illustrates the main results of the clinical studies conducted with dapagliflozin and empagliflozin that evaluated the impact of these drugs on the prognosis of patients with heart failure.[4-7,13,14]

Renal benefits of sodium-glucose cotransporter type 2 inhibitors

Impaired renal function is present in more than 30% of patients with heart failure and is associated with a poorer prognosis.[15] In addition, episodes of heart failure flare-ups result in an accelerated progression of renal damage. Therefore, reducing renal function decline and related adverse events may confer important prognostic benefits in patients with heart failure. An important finding in favour of the use of SGLT2-i is the evidence of slowed progression of kidney injury, measured as a decline in estimated glomerular filtrate (eGFR), and a lower incidence of renal adverse events, reduced by more than 50% in clinical trials conducted in patients with HFrEF.[6,7] The renal benefit associated with the use of SGLT2-i was confirmed by a recent meta-analysis[16] that included 13 RCTs with a total of more than 90 000 patients. In patients with chronic renal failure and with heart failure, SGLT2-i compared with placebo reduced the risk of kidney damage progression by 37% and acute kidney damage by 23%, with a similar benefit irrespective of baseline eGFR, which in any case was never <20 mL/min/1.73 m^2 in any clinical study, and irrespective of the presence or absence of diabetes mellitus. Furthermore, when SGLT2-i use was specifically tested in patients with chronic kidney disease (eGFR 30–90 mL/min/1.73 m^2 for canagliflozin[17]; 25–75 mL/min/1.73 m^2 for dapagliflozin[18]; and 20–45 mL/min/1.73 m^2 or 45–90 mL/min/1.73 m^2 with an albumin/creatinine ratio ≥200 for empagliflozin[19]), there was a significant reduction in the composite endpoint of renal disease progression and death from renal or cardiovascular causes. Overall, available evidence supports the use of SGLT2-i as a therapy to reduce the risk of renal damage progression and acute damage in both patients with chronic kidney disease and heart failure, irrespective of the presence of diabetes or renal function, for eGFR values that fall within the range of the inclusion criteria of clinical trials that have tested their efficacy and safety.

Practical indications for the use of sodium-glucose cotransporter type 2 inhibitors in patients with heart failure

In view of the robust evidence of a significant clinical benefit of SGLT2-i, dapagliflozin and empagliflozin have

Table 1 Randomized controlled trials evaluating the impact of dapagliflozin and empagliflozin on the prognosis of patients with heart failure

Clinical study (year)	Patient population (no. of patients included in the study)	Drug tested	Primary endpoint	Results
Studies evaluating cardiovascular safety in patients with type 2 diabetes mellitus				
EMPA-REG OUTCOME (2016)[4]	Patients with T2DM, cardiovascular disease, and eGFR > 30 mL/min/1.73 m^2	Empagliflozin 10 mg or 25 mg vs. placebo	Hospitalization for heart failure or cardiovascular death	HR 0.66; 95% CI, 0.55–0.79, $P < 0.001$
DECLARE-TIMI 58 trial (2019)[5]	Patients with T2DM, cardiovascular disease, or multiple risk factors and eGFR > 60 mL/min/1.73 m^2 ($n = 17\,160$)	Dapagliflozin 10 mg vs. placebo	Hospitalization for heart failure or cardiovascular death	HR 0.83; 95% CI, 0.73–0.95; P 0.005
Studies evaluating heart failure–related outcomes in patients with heart failure and EF <40%				
DAPA-HF (2019)[6]	Patients with heart failure, NYHA class ≥ II, and EF <40% ($n = 4744$)	Dapagliflozin 10 mg vs. placebo	Composite of heart failure worsening (hospitalization or need for intravenous therapy) or death from cardiovascular causes	HR 0.74; 95% CI, 0.65–0.85; $P < 0.001$
EMPEROR-Reduced (2020)[7]	Patients with heart failure, NYHA class ≥ II, and EF <40% ($n = 3730$)	Empagliflozin 10 mg vs. placebo	Composite of hospitalization for worsening heart failure or death from cardiovascular causes	HR 0.75; 95% CI, 0.65–0.86; $P < 0.001$
Studies evaluating heart failure–related outcomes in patients with heart failure and EF >40%				
EMPEROR-Preserved (2021)[13]	Patients with heart failure and EF > 40% ($n = 5988$)	Empagliflozin 10 mg vs. placebo	Composite of heart failure worsening (hospitalization or need for urgent care) or death from cardiovascular causes	HR 0.77; 95% CI, 0.67–0.87; $P < 0.0001$)
DELIVER (2022)[14]	Patients with heart failure and EF > 40% ($n = 62\,623$)	Dapagliflozin 10 mg vs. placebo	Composite of heart failure worsening (hospitalization or need for urgent care) or death from cardiovascular causes	HR 0.82; 95% CI, 0.73–0.92; $P < 0.001$

GFR, estimated glomerular filtration rate; EF, left ventricular ejection fraction; HR, hazard ratio; CI, confidence interval; NYHA, New York Heart Association functional class; T2DM, type 2 diabetes.

been included among the recommended treatments for reducing mortality and hospitalization risk in patients with HFrEF regardless of the presence of type 2 diabetes mellitus (class of recommendation I, level of evidence A).[2,3] Since clinical evidence in favour of the use of these drugs in patients with heart failure with intermediate or preserved ejection fraction were obtained after the publication of the latest ESC guidelines, these guidelines do not include SGLT2-i as a therapeutic option in patients with intermediate or preserved ejection fraction.[2] The American guidelines, which were published after the publication of the results of the EMPEROR-Preserved study,[13] consider the use of SGLT2-i also in patients with intermediate (41–49%) and preserved (>50%) ejection fraction, with the aim of reducing cardiovascular mortality and hospitalizations for heart failure (class IIa recommendation, level of evidence B; *Table 2*).[2,3] The European Medicines Agency (EMA) has approved the use of both dapagliflozin and empagliflozin in adult individuals (age >18 years) with heart failure and reduced ejection fraction (<40%).[20,21] More recently, the EMA has expressed a positive view of empagliflozin use in patients with ejection fraction >40%.[20] For both drugs, the recommended dosage is 10 mg/day and, unlike other drugs used in HFrEF, does not require titration. In order to benefit as early as possible from the favourable effects of SGLT2-i, these drugs should be used in combination with other drugs able to modify the prognosis of patients with HFrEF. The achievement of target doses of RASi/inhibitors of the angiotensin and neprilysin receptor, beta blockers, and mineralocorticoid receptor antagonists recommended by guidelines should not be a reason for late initiation of SGLT2-i.[22] In Italy, for the treatment of heart failure, reimbursement of SGLT2-i by the National Health System is allowed only if prescribed by authorized centres identified by the regions and requires the completion of a 'web-based' treatment plan.[23] Criteria for prescribing SGLT2-i include an ejection fraction <40% and a New York Heart Association functional class II or III.

Precautions

In clinical practice, the use of SGLT2-i should be considered, in all patients with HFrEF regardless of the presence of diabetes mellitus,[24] excluding patients in whom the drug is contraindicated. The presence of comorbidities or conditions that expose the patient to an increased risk of side effects should be evaluated carefully before the initiation of therapy (*Table 3*). More specifically, it is important to assess renal function and serum electrolytes and to calculate eGFR before starting treatment. Both dapagliflozin and empagliflozin can be used in patients with HFrEF and chronic renal failure with

Table 2 Indications for sodium–glucose cotransporter type 2 inhibitor use according to European Society of Cardiology and American College of Cardiology/American Heart Association guidelines on heart failure[2,3]

	2021 ESC guidelines		2022 ACC/AHA guidelines	
	Class[a]	Level[b]	Class[a]	Level[b]
Treatment with SGLT2-i is recommended in patients with HFrEF independently of the presence of DM2 to reduce the risk of hospitalization due to HF and cardiovascular mortality	I	A	I	A
In patients with HFmrEF or HFpEF, treatment with SGLT2-i may be useful in reducing the risk of hospitalization due to HF and cardiovascular mortality			II	A

ACC, American College of Cardiology; AHA, American Heart Association; DM2, type 2 diabetes mellitus; ESC, European Society of Cardiology; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; SGLT2-i, sodium-glucose cotransporter type 2 inhibitors.
[a]Class of recommendation.
[b]Level of evidence.

Table 3 Practical considerations for the use of sodium-glucose cotransporter type 2 inhibitors in patients with heart failure and reduced ejection fraction (adapted from McDonagh *et al.*)[2]

For whom and when?	Indications	Patients with HFrEF regardless of the presence of DM2
	Not recommended	Pregnancy or breastfeeding GFR < 20 or 25 mL/min/1.73 m^2 for empagliflozin and dapagliflozin, respectively Hypovolaemia or PAS < 95 mmHg DM1 for lack of data on efficacy and safety History of ketoacidosis
Which dosage?	Dapagliflozin	Starting/maintenance dose 10 mg once/day
	Empagliflozin	Starting/maintenance dose 10 mg once/day
How to use them?	Define renal function at the beginning of therapy and monitor it regularly Monitor blood glucose (especially in patients with DM) Identify any risk factors for ketoacidosis and remove them Monitor fluid balance regularly, particularly if the patient is older, taking diuretics, or frail	
Side effects	Glycosuria: susceptibility to genitourinary fungal infections Hypoglycaemia: use with caution in combination with insulin, sulfonylureas, and other insulin secretagogues Hypotension: assess the state of hydration and reduce or discontinue any current diuretic therapy Ketoacidosis: should be suspected in case of nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulties in breathing, confusion, and abnormal fatigue Necrotising fasciitis of the perineum or Fournier's gangrene	

DM1, type 1 diabetes mellitus; DM2, type 2 diabetes mellitus; eGFR, estimated glomerular filtrate; HFrEF, heart failure with reduced ejection fraction; PAS, systolic blood pressure.

eGFR <60 mL/min/1.73 m^2 without any dose adjustment. However, because of limited clinical data, it is not advisable to start treatment with dapagliflozin in patients with eGFR <25 mL/min/1.73 m^2 or with empagliflozin in cases of eGFR <20 mL/min/1.73 m.[2] Another important aspect to consider when starting treatment with SGLT2-i is the hydration/volaemia status of the patient and blood pressure values. The osmotic diuresis induced by these agents can result in a reduction in volaemia and a slight reduction in systolic and diastolic blood pressure values (by 4–6 and 1–2 mmHg, respectively).[25] These effects may be more pronounced in some groups of patients such as the elderly, patients with hyperglycaemia, and those treated with diuretics. In cases of volume depletion and/or hypotension, it is necessary to correct these conditions before starting treatment with SGLT2-i. In some cases, before starting treatment or during treatment, it may be appropriate to reduce the dosage of diuretics or antihypertensive agents. Patients should be informed about the need to maintain adequate fluid intake. Over the course of treatment, blood pressure and body weight should be monitored periodically, particularly in the first few weeks. In patients with mild or moderate hepatic impairment, there is no need for any variation dosage. In severe hepatic insufficiency, due to the increased SGLT2-i exposure, it is recommended that an initial dose of 5 mg/day be increased to 10 mg/day if the treatment is well tolerated. *Figure 1* shows the algorithm for the initiation of treatment with SGLT2-i in patients with type 2 diabetes mellitus. Since the hypoglycaemic effect of this drug class is related to plasma glucose concentrations, in patients with type 2 diabetes, the risk of hypoglycaemia is low if SGLT-is are not used in combination with insulin or insulin secretagogue drugs. Patients treated with sulfonylureas or insulin should be managed in collaboration with diabetologists in order to appropriately reduce the dosage of hypoglycaemic agents concomitantly with the initiation of SGLT2-i. In patients treated with metformin, dipeptidyl peptidase 4 inhibitors, or glitazones, if glycaemic levels are above the recommended target and there is no tendency for hypoglycaemia in the patients' history, there is generally no need to change the dosage of these agents.

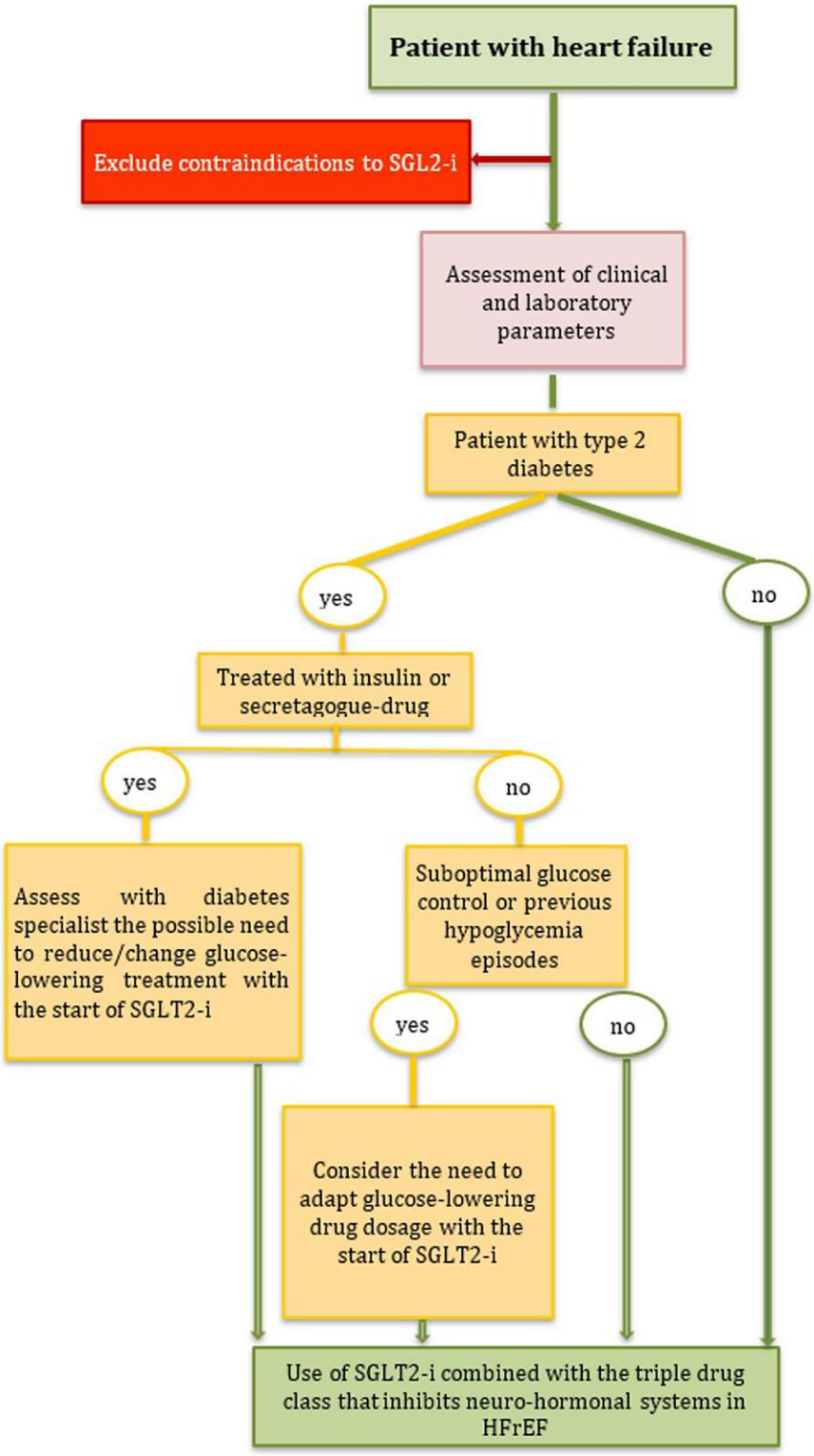

Figure 1 Therapeutic algorithm for SGLT2-i use in patients with heart failure. Modified from Di Fusco *et al.*[22]

Follow-up

The primary care physician should be notified about the start of SGLT2-i medication. Indeed, clinical-laboratory parameters, such as body weight, blood pressure, hydration status, renal function, electrolytes, and blood sugar level, should be periodically evaluated. In diabetic patients, blood sugar levels should be regularly examined. As highlighted in a recent ANMCO position paper, in the management of patients with heart failure

treated with SGLT2-i, the role of the N-terminal fragment of type B natriuretic propeptide in prognosis and as an index of response to therapy is not yet well defined.[26]

During follow-up, signs and symptoms of dehydration/hypovolaemia should be investigated, such as asthenia, orthostatic hypotension, and weight loss >1 kg in 24 h or >2 kg in 1 week. If volume depletion is suspected, renal function and serum electrolytes should be evaluated. In older patients or those receiving high doses of diuretics, these parameters should be regularly checked.

It is crucial to warn patients receiving SGLT2-i about the possibility of genitourinary infections and the possible signs and symptoms associated with these infections. Patients should refrain from beginning restrictive carbohydrate diets and drinking too much alcohol while receiving this therapy. Gliflozins should be discontinued 2–3 days before any interventional or surgical procedure requiring prolonged fasting.

Side effects

The main side effect of SGLT2-i is genital fungal infection (candida vulvovaginitis and balanitis), which is more common in females and those with a history of previous genital infections. These are generally mild-to-moderate infections with a good response to conventional therapies, including local antifungals, and very rarely require drug suspension, except in cases of pyelonephritis and urinary sepsis. Severe infections can be treated with oral fluconazole.

Necrotizing fasciitis of the perineum, also known as Fournier's gangrene, is a rare but significant and sometimes fatal adverse event. Patients should be advised to contact their doctor if they experience discomfort, soreness, erythema, or swelling in the genital or perineal area, along with fever or malaise.

Only a few severe cases of diabetic ketoacidosis have been documented.[27] This risk increases with reduced food intake, dehydration, increased insulin requirements, and acute illness. Non-specific symptoms can be observed, including nausea, vomiting, anorexia, stomach discomfort, excessive thirst, breathing difficulties, confusion, and unusual fatigue or sleepiness. If these symptoms are present, patients should be assessed for ketoacidosis immediately, and SGLT2-i therapy discontinued, regardless of blood glucose levels.

Patients who develop severe conditions, such as skin ulcers, infections, osteomyelitis, or gangrene, should be advised to discontinue SGLT2-i. Another potential SGLT2-i side effect is polyuria, which can cause intravascular volume contraction and hypotension.

Conclusions

Sodium–glucose cotransporter 2 inhibitor represents the fourth pillar in the therapeutic armamentarium to improve the prognosis of patients with HFrEF. Although this class of drugs is well tolerated, it is crucial to be aware of any potential side effects and health issues that, if not properly treated, could expose patients to a higher risk of adverse outcomes.

Funding

This paper was published as part of a supplement financially supported by the Italian National Association of Hospital Cardiologists (ANMCO).

Conflict of interest: The authors declare no conflict of interest.

Disclaimer This Position Paper was originally published in the Italian language as 'Position paper ANMCO: Guida pratica ANMCO all'impiego degli inibitori del cotrasportatore sodio-glucosio di tipo 2 nei pazienti con scompenso cardiaco', in the official journal of the Italian Federation of Cardiology (IFC) 'Giornale Italiano di Cardiologia', published by Il Pensiero Scientifico Editore. This paper was translated by a representative of the Italian Association of Hospital Cardiologists (ANMCO) and reprinted with permission of IFC and Il Pensiero Scientifico Editore.

Data availability

No new data were generated or analysed in support of this research.

References

1. Lippi G, Sanchis-Gomar F. Global epidemiology and future trends of heart failure. *AME Med J* 2020;**5**:15.
2. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm A, *et al*. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021;**42**:3599–3726.
3. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, *et al*. 2022 AHA/ACC/HFSA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol* 2022;**79**:1757–1780.
4. Fitchett D, Zinman B, Wanner C, Lachin JM, Hantel S, Salsali A, *et al*. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME trial. *Eur Heart J* 2016;**37**:1526–1534.
5. Kato ET, Silverman MG, Mosenzon O, Zelniker TA, Cahn A, Furtado RHM, *et al*. Effect of dapagliflozin on heart failure and mortality in type 2 diabetes mellitus. *Circulation* 2019;**139**:2528–2536.
6. McMurray JJ, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, *et al*. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019;**381**:1995–2008.
7. Packer M, Anker SD, Butler J, Filippato J, Pocock SJ, Carson P, *et al*. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med* 2020;**383**:1413–1424.
8. Gronda E, Iacoviello M, Benvenuto M, Valenti C, Navazio A, Caldarola P, *et al*. I meccanismi d'azione degli inibitori del cotrasportatore sodio-glucosio di tipo 2 ed i loro effetti benefici sull'assetto funzionale di cuore e rene [The mechanisms mediating the favorable effects of sodium-glucose cotransporter 2 inhibitors on cardiorenal function]. *G Ital Cardiol (Rome)* 2022;**23**:854–871.
9. Cherney DZ, Perkins BA, Soleymanlou N, Har R, Fagan N, Johansen OE, *et al*. The effect of empagliflozin on arterial stiffness and heart rate variability in subjects with uncomplicated type 1 diabetes mellitus. *Cardiovasc Diabetol* 2014;**13**:28.
10. Mazer CD, Hare GMT, Connelly PW, Johansen RE, Shehata N, Quan A, *et al*. Effect of empagliflozin on erythropoietin levels, iron stores, and red blood cell morphology in patients with type 2 diabetes mellitus and coronary artery disease. *Circulation* 2020;**141**:704–707.
11. Joshi SS, Singh T, Newby DE, Singh J, Filippatos G, Ferreira JP, *et al*. Sodium-glucose co-transporter 2 inhibitor therapy: mechanisms of action in heart failure. *Heart* 2021;**107**:1032–1038.
12. Gronda E, Colivicchi F, Zuccalà G. Letter by Gronda, et al regarding article, "Effect of Empagliflozin on Worsening Heart Failure Events in Patients With Heart Failure and Preserved Ejection Fraction: EMPEROR-Preserved Trial". *Circulation* 2022;**145**:e839–e840.
13. Packer M, Butler J, Zannad F, Filippatos J, Ferreira JP, Pocock SJ, *et al*. Effect of empagliflozin on worsening heart failure events in patients with heart failure and preserved ejection fraction: EMPEROR-preserved trial. *Circulation* 2021;**144**:1284–1294.

14. Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, *et al*. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med* 2022;**387**: 1089–1098.
15. Damman K, Valente MA, Voors AA, O'Connor CM, van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. *Eur Heart J* 2014;**35**:455–469.
16. The Nuffield Department of Population Health Renal Studies Group* and the SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists'. Consortium impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. *Lancet* 2022;**400**:1788–1801.
17. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, *et al*. Canagliflozin and renal outcomes in type 2, diabetes and nephropathy. *N Engl J Med*. 2019;**380**:2295–2306.
18. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Correa-Rotter R, Chertow GM, Greene T, *et al*. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med* 2020;**383**:1436–1446.
19. The EMPA-KIDNEY Collaborative Group, Herrington WG, Staplin N, Wanner C, Green JB, Hauske SJ, *et al*. Empagliflozin in patients with chronic kidney disease. *N Engl J Med* 2022;**388**:117–127.
20. Jardiance summary of product characteristics. Disponibile online: Jardiance, INN-Empagliflozin (europa.eu) (accesso 30 Ottobre 2022)
21. European Medicines Agency. Forxiga summary of product characteristics. Forxiga, INN-dapagliflozin (europa.eu) (ultimo accesso 25-11-2022)
22. Di Fusco SA, Gronda E, Mocini E, Lucà F, Bisceglia I, De Luca L, *et al*. ANMCO statement on the use of sodium-glucose cotransporter 2 inhibitors in patients with heart failure: a practical guide for a streamlined implementation. *Eur Heart J Suppl* 2022;**24**:C272–C277.
23. Gazzetta Ufficiale della Repubblica Italiana 2022; anno163, numero 3. Online aivalable: pdf (gazzettaufficiale.it) (accesso il 02–11–2022)
24. Rosano G, Iacoviello M, Filardi PP. La "serendipity" degli inibitori del co-trasportatore sodio-glucosio di tipo 2: un nuovo paradigma nello scompenso cardiaco con frazione di eiezione ridotta [Serendipity of sodium-glucose co-transporter 2 inhibitors: a new paradigm in the management of heart failure with reduced ejection fraction]. *G Ital Cardiol (Rome)* 2021;**22**:277–283.
25. Vardeny O, Vaduganathan M. Practical guide to prescribing sodium-glucose cotransporter 2 inhibitors for cardiologists. *JACC Heart Fail* 2019;**7**:169–172.
26. Gronda E, Napoli C, Iacoviello M, Urbinati S, Caldarola P, Mannucci E, *et al*. Position paper ANMCO: l'impiego degli inibitori del co-trasportatore sodio-glucosio di tipo 2 nella prevenzione e cura dell'insufficienza cardiaca nei soggetti diabetici e nei portatori di insufficienza cardiaca, diabetici e non diabetici [ANMCO position paper: sodium-glucose co-transporter 2 inhibitors for the prevention of heart failure in diabetic patients and for the treatment of heart failure patients with and without diabetes]. *G Ital Cardiol (Rome)* 2021;**22**:675–687.
27. Milder TY, Stocker SL, Day RO, Greenfield JR. Potential safety issues with use of sodium-glucose cotransporter 2 inhibitors. *Particularly in people with type* 2 diabetes and chronic kidney disease. *Drug Saf* 2020;**43**:1211–1221.