


# Egyptian expert opinion for the use of sodium-glucose cotransporter-2 inhibitors in patients with heart failure with reduced ejection fraction

Magdy Abdelhamid<sup>1\*</sup> , Hossam Kandil<sup>1</sup>, Mahmoud Hassanin<sup>2</sup>, Sameh Shaheen<sup>3</sup>, Mohamed Sobhy<sup>2</sup>, Adel ElEtreby<sup>3</sup>, Hosam Hasan-Ali<sup>4</sup>, Hala Mahfouz<sup>5</sup>, Gamila Nasr<sup>6</sup>, Islam Shawky<sup>7</sup>, Sameh Emil<sup>8</sup>, Mohamed ElSetiha<sup>9</sup>, Mohamed Hasssan<sup>1</sup>, Yasser Sadek<sup>10</sup>, Mohamed Abdelghany Karim<sup>4</sup>, Ayman Asham<sup>11</sup>, Mohamed Ghaleb<sup>12</sup>, Ahmad Samir<sup>1</sup> and Khaled Shokry<sup>8</sup>

<sup>1</sup>Faculty of Medicine, Kasr Al Ainy, Cardiology Department, Cairo University, Cairo, Egypt; <sup>2</sup>Faculty of Medicine, Alexandria University, Alexandria, Egypt; <sup>3</sup>Faculty of Medicine, Ain Shams University, Cairo, Egypt; <sup>4</sup>Faculty of Medicine, Assiut University, Assiut, Egypt; <sup>5</sup>Faculty of Medicine, Menoufia University, Shibin Al Kawm, Egypt; <sup>6</sup>Faculty of Medicine, Suiz Canal University, Ismailia, Egypt; <sup>7</sup>Faculty of Medicine, Al Azhar University, Cairo, Egypt; <sup>8</sup>Armed Forces College of Medicine, Cardiology Department, Cairo, Egypt; <sup>9</sup>Faculty of Medicine, Tanta University, Tanta, Egypt; <sup>10</sup>Faculty of Medicine, Helwan University, Helwan, Egypt; <sup>11</sup>Faculty of Medicine, Aswan University, Aswan, Egypt; and <sup>12</sup>Cardiology Unit, Research Institute of Ophthalmology, Cairo, Egypt

## Abstract

Sodium-glucose cotransporter-2 inhibitor (SGLT2i) in patients with type 2 diabetes reduces the risk of serious heart failure events, specifically the risk of hospitalization for heart failure, and cardiovascular death. The benefit is most apparent in patients with a heart failure with reduced ejection fraction (HFrEF). Dapagliflozin and empagliflozin reduced the risk of cardiovascular death and hospitalizations for heart failure in patients with established HFrEF, including those without diabetes. Considering the magnitude of the problem and the expected benefit on the target population, an Egyptian consensus document was conducted to demonstrate the importance of and the critical knowledge needed for effective and safe implementation of SGLT2i in the daily practice for the management of patients with HFrEF.

**Keywords** Sodium-glucose cotransporter-2 inhibitor; Heart failure with reduced ejection fraction

Received: 27 October 2021; Revised: 24 December 2021; Accepted: 5 January 2022

\*Correspondence to: Magdy Abdelhamid, Faculty of Medicine, Kasr Al Ainy, Cardiology Department, Cairo University, Cairo, Egypt.  
Email: magdyabdelhamid@hotmail.com

## Heart failure and diabetes mellitus: the deadly duo

An estimated 64.3 million people are living with heart failure (HF) worldwide.<sup>1</sup> In developed countries, the prevalence of known HF is generally estimated at 1% to 2% of the general adult population. A meta-analysis—based on echocardiographic screening studies in the general population—showed that the prevalence of ‘all type’ HF in developed countries is around 11.8% in those aged 65 years and over.<sup>2</sup> To date, there are no population-based studies estimating the prevalence of HF in Egypt and North Africa.

Type 2 diabetes mellitus (T2DM) and HF often occur concomitantly, and each disease independently increases the risk for the other. In HF cohorts, including both HF with reduced

ejection fraction (HFrEF) and HF with preserved ejection fraction, the prevalence of DM ranges from 10% to 47%.<sup>3</sup> Furthermore, glucose-lowering medications may influence the risk of HF development and progression. In the Framingham Heart Study, DM was associated with a nearly two-fold increase in the risk of incident HF in men and a four-fold increase in women, even after adjustment for other cardiovascular (CV) risk factors.<sup>4</sup>

Egypt ranked ninth in the top 10 countries of number of people with diabetes aged 20–79 years with a national prevalence rate of 15.2% (8.9 million).<sup>5</sup> About 53.3% of all deaths from DM in Middle East North Africa region occurred in people under 60 years, making it the region with the second highest proportion of diabetes-related deaths under 60 years of age.<sup>6</sup>

In a recent registry of HF in Egypt, the HF patients were much younger—the median age was 61 years compared with median age of 73 years of their European counterparts. Female patients comprised one-third of the cohort. HF with preserved ejection fraction was present in 22% of patients. DM was reported in 45.4% of patients enrolled in this registry. Ischaemic heart disease was the primary aetiology in 68% of patients. The all-cause in-hospital and 1 year mortality were 5% and 27%, respectively.<sup>7,8</sup>

## The unmet needs in managing type 2 diabetes mellitus in heart failure patients

Through the past decades, diabetes management in patients with CV disease was significantly flawed for many reasons. First, patients with CV disease were often excluded from major trials of non-insulin therapies. Second and more importantly, the general philosophy was very glucocentric (i.e. weighing the benefit of a certain drug solely by its Hb1Ac reduction potency).<sup>9</sup> The latter concept was radically challenged when a meta-analysis of 43 trials of rosiglitazone (despite its glycaemia control) showed a significant increase in incidence of myocardial infarction (MI) and a trend to increased CV death.<sup>10</sup> Moreover, a meta-analysis of more than 24 000 individuals reported that the use of insulin itself for T2D was also associated with a 27% increase in all-cause mortality and 23% increase in hospitalization for HF.<sup>11</sup>

Since then, the inter-relation between antidiabetic agents and CV disease was looked as a more complex interplay than simply the glycaemic control, and an era of dedicated CV outcome trials (CVOTs) for the antidiabetic medications was urged to commence.

Major adverse CV events were the first to be in the focus of CVOT, possibly because of representing well-defined hard endpoints (CV death, non-fatal MI, and non-fatal stroke) and because they were presumed at that era to be the most influenced by diabetes and antidiabetic medications at that era. The dipeptidyl peptidase-4 inhibitors and the glucagon-like peptide-1 agonists showed consistent data for safety (or benefit) regarding major adverse CV events, like what was seen in EXAMINE (alogliptin), LEADER (liraglutide), SUSTAIN-6 (semaglutide), and REWIND (dulaglutide)<sup>9</sup> trials. However, saxagliptin increased the incidence of new HF by 27% in the SAVOUR-TIMI 53 trial.<sup>12</sup>

## Sodium-glucose cotransporter-2 inhibitor, the missing block in T2D therapies

Unfortunately, from the HF perspectives, such effects remained for long time an unmet need. Till 2015 and before

the EMPAREG results, most of what we had to treat T2DM either increased HF hospitalizations or at the best expectations were neutral. The first appreciable clinical benefit for HF patients was with the evolution of the sodium-glucose cotransporter-2 inhibitors (SGLT2is) class: empagliflozin in the EMPAREG trial. In EMPAREG trial, empagliflozin has showed substantial reduction in HHF and death.<sup>13</sup> This was shortly followed by similar results for dapagliflozin in DECLARE-TIMI 58, supporting a class effect.<sup>14</sup>

Soon later, a renoprotective effect was clearly appreciated with this novel antidiabetic class and then followed by proven expansion of the HF and renal benefits equally to diabetics and non-diabetics.<sup>15</sup> The SGLT2i class that was originally directed to treat T2DM is nowadays revolutionizing the management of HFrEF or chronic kidney disease (CKD) and became one of the main pillars in their management.

## Rationale for use of sodium-glucose cotransporter-2 inhibitor in patients with heart failure with reduced ejection fraction

Guideline-directed medical therapy (GDMT) for HFrEF has evolved significantly throughout the past decade. Yet probably more improvements are needed acknowledging that the 5 year mortality rate of 50% is endangering 64 million patients worldwide.<sup>16</sup>

Sodium-glucose cotransporter-2 inhibitor might have a promising role to bridge that gap. While SGLT2i class has been known to be an effective oral antidiabetic class for years from the data extracted from EMPAREG-OUTCOME, CANVAS, and DECLARE-TIMI trials, their CV benefits were observed to be independent from their glycaemic control and extending beyond the diabetic status. This was proved for the first time in history in DAPA-HF trial showing significant reduction in HHF and CV mortality in HFrEF patients with and without T2DM. Such CV benefits of the class that are independent from diabetes status were confirmed by the EMPEROR-Reduced and CANVAS trial and meta-analyses that followed.<sup>13,14,17–19</sup>

Since the early 2000s, the main stay for treating HFrEF was blocking renin angiotensin aldosterone axis with an angiotensin-converting enzyme inhibitors (ACEI) or an angiotensin II receptor blocker, and a mineralocorticoid receptor antagonists (MRAs) in addition to blocking beta adrenergic receptors, with one of the guidelines directed and approved agents.

In 2016, American College of Cardiology/American Heart Association similar to the European Society of Cardiology (ESC) released a guidelines update on HF pharmacological therapy to include angiotensin receptor-neprilysin inhibitor

(ARNI) for HFrEF patients who remain symptomatic despite maximally tolerated doses of the basic pharmacological agents and sinoatrial node modulator (ivabradine) for symptomatic patients with heart rate more than 70 beats per minute.<sup>20,21</sup>

In 2021, and after the consistent evidence of their clinical benefit, the American College of Cardiology released an expert pathway that included SGLT2i as a new pillar in HFrEF management.<sup>22</sup> This was followed by the ESC release of the 2021 consensus for HFrEF patients profiling, then the guidelines for management of acute and chronic HF that modified the previous guidelines into a novel approach tailored for each patient profile separately, and recommending the use of SGLT2i in a new low level of estimated glomerular filtration rate (eGFR) for its renal protection effect (e.g. there is evidence of benefit from dapagliflozin also in patients with eGFR < 20 mL/min/1.73 m<sup>2</sup>).<sup>16</sup>

The unmet needs and rationale for the use of SGLT2i in HFrEF patients can be summarized in the following:

- Prevention of HFrEF in T2DM patients with early use of SGLT2i in T2DM patients.
- Despite the reduction in mortality rates provided by the current treatment drugs, there is still poor prognosis for HFrEF patients.

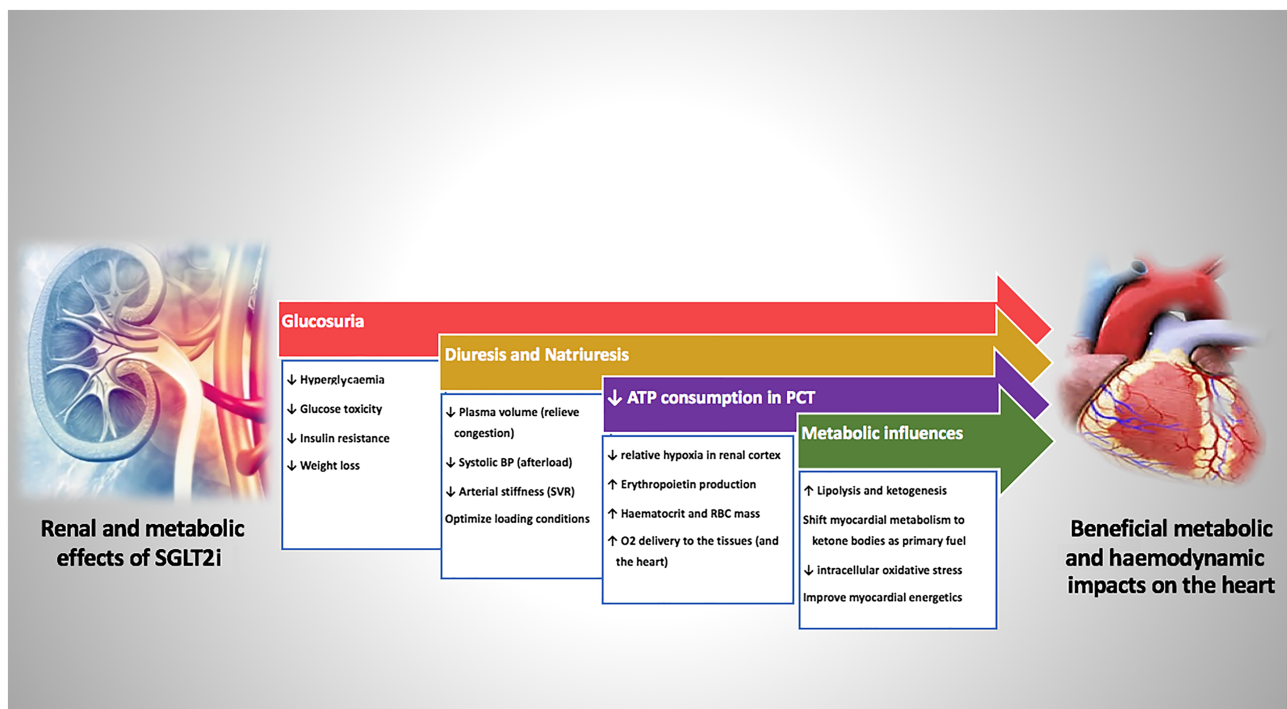
- There are no drugs that positively influenced the cardiorenal syndrome and the decline of renal functions in HFrEF patients except SGLT2i.<sup>23</sup>
- Guidelines are not well implemented in the clinical practice yet.<sup>16</sup>
- The high cost of ARNI in the Egyptian context.<sup>24</sup>

Thus, SGLT2i is an addition that can improve the patients' quality of life and prognosis if added to the proper HFrEF medical therapy.

## Potential mechanisms of benefit with sodium-glucose cotransporter-2 inhibition

The exact mechanisms by which SGLT2i exert their benefits in these populations are not completely understood. It has been postulated that SGLT2i improves CV outcomes through several metabolic, cardioprotective, and nephroprotective pathways<sup>25</sup> (*Figure 1*): (i) SGLT2i blocks SGLT2 protein located in the proximal convoluted tubule of the nephron, and the latter is responsible for reabsorption of approximately 90% of filtered glucose. Accordingly, they increase urinary glucose and sodium excretion, which subsequently reduce plasma

**Figure 1** Potential mechanisms of benefit of SGLT2 inhibition in patients with heart failure with reduced ejection fraction. ATP, adenosine triphosphate; BP, blood pressure; SGLT2i, sodium-glucose cotransporter inhibitor; SVR, systemic vascular resistance.



volume (preload) and blood pressure (BP) (afterload), translating into optimization of ventricular loading conditions. (ii) Weight reduction due to increased glucagon–insulin ratio, increased lipolysis, and improved glycaemic control. (iii) Reduced adenosine triphosphate consumption in proximal convoluted tubule and by decreasing energy demands needed for glucose reabsorption, thus reducing the relative hypoxia in renal cortex, which leads to reversion of myofibroblast to erythropoietin-producing fibroblast. This leads to increases in renal erythropoietin production, red blood cell mass, and haematocrit, with their subsequent beneficial effects on HF symptoms and prognosis. (iv) Improved myocardial energetics and a shift in cardiac metabolism away from fatty acids and glucose oxidation towards more oxygen-efficient ketone bodies may be other plausible mechanisms, thereby improving cardiac efficiency.<sup>26</sup> (v) Improved ionic homeostasis in myocardium reduced oxidative stress and inflammation. (vi) Altered adipokine regulation. SGLT2i reduces serum leptin and increases adiponectin concentrations, potentially offering some cardioprotection.

## Sodium-glucose cotransporter-2 inhibitor and cardiovascular outcome

Large CVOTs in patients with T2DM have shown that SGLT2i improves CV and renal outcomes. SGLT2i reduces the risk of hospitalization for HF [a relative risk reduction (RRR) of at least 30%], slows the progression of renal disease (RRR of at least 40%), and reduces CV death (an RRR of 14%).<sup>13,14,27</sup> These benefits were observed in patients with and without a previous history of HF.<sup>28</sup> However, patients with known HF comprised only small proportions of the study populations of these trials.

### Two major outcome trials

DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) and Emperor-reduced (EMPagliflozin outcomE tRial in Patients with chrOnic heaRt Failure with Reduced Ejection Fraction) trials were conducted assessing the effect of SGLT2 inhibitors in patients with a broad spectrum of severity of HFrEF with or without diabetes.

#### *The DAPA-HF trial*

The DAPA-HF trial was the first outcome trial specifically designed to assess the effect of SGLT2 inhibitors in 4744 patients with HFrEF (EF < 40% and New York Heart Association class ≥ II, NT pro-BNP ≥ 600 pg/dL) with or without diabetes. Patients with systolic BP less than 95 mmHg,

and eGFR less than 30 mL/min/1.73 m<sup>2</sup> were excluded.<sup>18</sup> Patients were randomized to receive either dapagliflozin 10 mg or placebo in addition to best guideline-directed medical and device therapies. At baseline, 45% of enrolled patients have T2DM. The primary outcome was a composite of CV death and worsening HF (hospitalization for HF or urgent HF visit). Over a median follow-up period of 18.2 months, the primary composite endpoint was reduced by 26% RRR in dapagliflozin group ( $P < 0.001$ ). The demonstrated clinical benefits were similar in patients with diabetes and without diabetes.

#### *EMPEROR-reduced trial*

EMPEROR-Reduced trial was designed to study the same target population of DAPA-HF study but was enriched for sicker patients with markedly reduced ejection fraction and elevated natriuretic peptide concentrations. Patients with systolic BP less than 95 mmHg and eGFR less than 30 mL/min/1.73 m<sup>2</sup> were excluded. The study randomized 3730 patients to receive either empagliflozin 10 mg or placebo in addition to best guidelines directed medical and device therapies. The trial included ~50% of patients without T2DM, 73% had left ventricular ejection fraction < 30%, 79% had N-terminal B-type natriuretic peptide level ≥ 1000 pg/mL, and almost a half of patients had significant renal dysfunction at baseline eGFR of 20 to 60 mL/min/1.73 m<sup>2</sup>. The primary endpoint was a composite of CV death or hospitalization for HF. Over a median follow up of 16 months, primary outcome was reduced by 25% RRR in empagliflozin group ( $P < 0.001$ ). The effect of empagliflozin on the primary outcome was consistent in patients regardless of the presence or absence of diabetes.<sup>19</sup>

A meta-analysis of seven randomized trials including 16 820 HF patients ( $N = 8884$  in the SGLT2 inhibitor arms;  $N = 7936$  in the placebo arms) has been recently published.<sup>29</sup> The HFrEF subpopulation comprised 11 381 patients (67%) of the studied population. Compared with placebo, SGLT2i significantly reduced the risk for the composite endpoint of first HF hospitalization or CV death [hazard ratio (HR): 0.77 (0.72–0.83);  $P < 0.001$ ], time to first HF hospitalization [HR: 0.71 (0.64–0.78);  $P < 0.001$ ], CV death [HR: 0.87 (0.79–0.96);  $P = 0.005$ ], and all-cause mortality [HR: 0.89 (0.82–0.96);  $P = 0.004$ ]. These findings remained consistent when the HFrEF population was analysed separately and also when patients were stratified according to DM status. No increase in the risks of hypovolaemia, hyperkalaemia, or hypotension was seen with SGLT2i compared with placebo. The incidence of treatment-emergent serious adverse events [rate ratio (RR): 0.88 (0.84–0.91);  $P < 0.001$ ] and risk of acute kidney injury (AKI) [RR: 0.63 (0.45–0.87);  $P = 0.006$ ] were significantly lower in the SGLT2i arm.<sup>29</sup>

All these data establish that, independent of diabetes status and glycaemic effects, SGLT2i as a class is very well-tolerated

and highly effective in reducing CV death and hospitalization for HF and in improving quality of life in HFrEF population.

As a result, SGLT2i has qualified to place themselves as a new key component of goal-directed medical therapy in HFrEF.

## Safety

Sodium-glucose cotransporter-2 inhibitor has a well-defined safety profile based on data obtained from numerous clinical trials, including CVOTs and post-marketing pharmacovigilance reporting.<sup>13,14,17</sup> Adverse events including risk of genital mycotic infections and volume depletion-related events are consistent with the mechanism of action of this drug class. However, several emergent (albeit infrequent) serious safety issues have also been reported. In their respective CVOTs, the proportion of patients with reported diabetic ketoacidosis was similar in the empagliflozin or canagliflozin arms compared with their placebo counterparts, but it was higher for dapagliflozin. Canagliflozin may be associated with an increased risk of bone fractures and lower limb amputations; however, data were found to be inconclusive. The increased risk of bone fractures and lower limb amputations reported with canagliflozin in CANVAS (which remains largely unexplained)<sup>17</sup> is not confirmed in most other trials or observational studies, where data with canagliflozin, dapagliflozin, and empagliflozin do not refer to an appreciable class effect.

There is no evidence linking SGLT2i with an increased risk of cancer, but these agents, particularly dapagliflozin, should be used with caution in patients with haematuria or history of bladder cancers. Post-marketing reports of AKI have occurred in patients receiving SGLT2i, yet cases identified in recent CVOTs occurred with similar frequency in SGLT2i and placebo groups.

Common adverse events associated with SGLT2i (such as genital infections or volume depletion) are generally mild and manageable by patients or by primary care physicians, and the risk of rare events (such as ketoacidosis) can be minimized by appropriate patient selection and early recognition of symptoms. When selecting treatment, it is important that clinicians weigh the known risks of SGLT2i against their proven benefits, including the reduction of adverse CV and renal outcomes. These adverse events should not mask the overall CV and renal benefits of SGLT2is, especially in patients with T2DM at high CV risk.

Mild genital mycotic infections are the most common adverse events, whereas the risk of urinary tract infections is only marginally increased.

## Defining the targets of sodium-glucose cotransporter-2 inhibitor in heart failure with reduced ejection fraction management

There is growing body of evidence on the benefits of SGLT2i therapy for patients with HFrEF irrespective of having T2DM or not and irrespective of being on ARNI or not. However, practically, the prescription rate is still low, especially among patients most likely to attain the benefits from cardiorenal protective effects.<sup>30</sup> Several possible restraints contribute to the low SGLT2i prescription rate that include physicians hesitancy, lack of cardiologists' experience with their use, treatment inertia, elevated drug cost, and others. Thus, it is very prudent to identify as many as possible of these gaps aiming to find the appropriate corrective actions.

- 1 HFrEF and non-diabetic: It is recommended to use SGLT2i in all HFrEF patients irrespective of having T2DM or not, provided there are no contraindication (e.g. type 1 diabetes mellitus, diabetic ketoacidosis, pregnancy, and hypersensitivity to drug type). In the DAPA-HF trial, dapagliflozin reduced worsening of HF and CV death by 26% in patients with ejection fraction of  $\leq 40\%$ .<sup>18</sup> Similarly, empagliflozin in EMPEROR-Reduced trial decreased the primary outcome of CV death and HFH by 25%.<sup>19</sup> Non-diabetic patients represent 55% in DAPA-HF and 50% in EMPEROR-Reduced
- 2 HFrEF and chronic kidney disease: In albuminuric kidney disease (albuminuria of  $\geq 200$  mg/g of creatinine plus eGFR of 25–90 mL/min/1.73 m<sup>2</sup>), canagliflozin decreased the primary cardiorenal endpoint by 30% as evidenced by CRE-DENCE trial in patients with diabetic kidney disease.<sup>31</sup> In the DAPA-CKD trial, dapagliflozin was evaluated in albuminuric kidney disease (albuminuria  $\geq 200$  mg/day plus eGFR of 25–75 mL/min/1.73 m<sup>2</sup>), irrespective of T2DM status. One-third of the patients did not have T2DM, and the cardiorenal benefits of dapagliflozin were similar among patients with non-diabetic and diabetic kidney disease. The clinical benefits on CVD/HF and other CV outcomes for dapagliflozin compared with placebo were maintained among patients with and without known CV disease at baseline.<sup>18,32</sup> HFrEF patients with chronic kidney disease constituted 40–50% of the DAPA-CKD population, regardless diabetes is present or not. Dapagliflozin reduced the primary cardiorenal endpoint by 39% compared with placebo similarly in diabetic and non-diabetic kidney disease.<sup>19</sup>

3 HFrEF and type-2 diabetes mellitus: In T2DM and hyperglycaemia, several professional society guidelines recommend using SGLT2i as either first-line therapy or as an add-on therapy to metformin, for management of hyperglycaemia in patients with T2DM for their unprecedented cardioprotective and renoprotective effects (Class Ia recommendation).<sup>33–35</sup>

## Approach to prescribing of sodium-glucose cotransporter-2 inhibitors in heart failure with reduced ejection fraction

### Pre-initiation screening

Sodium-glucose cotransporter-2 inhibitor can be prescribed for all HFrEF patients, with or without T2DM, who have no contraindication to SGLT2i, are haemodynamically stable, and not on regular dialysis. It is recommended to initiate SGLT2i in HFrEF when eGFR  $\geq 60$  mL/min/1.73 m<sup>2</sup> (ertugliflozin) and  $\geq 30$  mL/min/1.73 m<sup>2</sup> (dapagliflozin, empagliflozin, and canagliflozin). Prior to initiation of SGLT2i, the patient's BP, volume status, and glycaemic control must be carefully assessed. SGLT2i should not be initiated in hypotensive/hypovolemic patients. In these patients, antihypertensive/diuretic agents may need to be modified or reduced, while in the latter, other diuretics doses are to be re-evaluated prior to SGLT2i initiation. The natriuretic (and BP lowering) effect of SGLT2i is modest, often resulting in ~3–5 mmHg reduction in systolic BP. Generally, SGLT2i can be added on top of the usual GDMT for HF as there are no treatment interactions.<sup>31</sup>

### Drug selection

Sodium-glucose cotransporter inhibitor-related benefits with respect to reduction of HFH and mortality appear relatively consistent for dapagliflozin, empagliflozin, and canagliflozin. They appear to have broadly similar CV and renal benefits. The choice of an individual agent should be made after appropriate patient–clinician discussion of benefits and potential risks. In patients with T2DM, SGLT2is are recommended (Class Ia recommendation) as a first-line therapy to lower risk of HFH, while metformin should be considered in patients with DM and HF if eGFR  $> 30$  mL/min/1.73 m<sup>2</sup>.<sup>35</sup>

### Dose titration

There have not been robust evidence yet on a graded dose response regarding CV and renal effects, although a higher

dose of SGLT2i can be used to improve glycaemic control. It is critical to realize that glucose-lowering potency of SGLT2i declines at lower eGFR values. Based on the evidence from CREDENCE and DAPA-CKD trials, once the SGLT2i therapy is initiated at the recommended level of eGFR, then it can be continued till the patient needs dialysis therapy.<sup>32</sup> All SGLT2is (dapagliflozin 10 mg PO/day, empagliflozin 10 mg PO/day, canagliflozin 100 mg PO/day, and ertugliflozin 5 mg PO/day) are preferably prescribed once daily in the morning.

### Patient counselling

Counselling regarding genital/perineal hygiene, orthostatic hypotension, foot examination, and symptoms of diabetic ketoacidosis is of pivotal importance to be discussed prior to drug initiation and to be discussed periodically in follow-up visits.<sup>36</sup>

### Patient monitoring

Sodium-glucose cotransporter inhibitor therapy can initially cause an acute drop in eGFR; however, subsequently, the decline in eGFR is attenuated with resumption of SGLT2i therapy. In the absence of haemodynamic instability or an alternate cause for AKI, the initial decline in eGFR (of up to 30%) following SGLT2i initiation is likely due to reduction in intraglomerular pressure.

Periodic monitoring of the kidney functions over 2–4 weeks from commencing treatment can help distinguish whether the decline in eGFR is due to the haemodynamic intraglomerular effects of SGLT2i or due to AKI, as the former is not progressive in contrast to the latter. In the absence of haemodynamic instability, SGLT2i do not increase the risk of AKI. In fact, an overall reduction in AKI has been observed with SGLT2i use.<sup>37</sup> Patients must be advised to hold SGLT2is when their oral intake of food and water is restricted due to a planned surgery or due to an underlying illness in order to minimize risks of hypovolemia, hypotension and diabetic ketoacidosis. This has been referred to as the 'Sick-day Rule'.

Serial monitoring of renal function, body weight, BP, and symptoms on regular and periodic basis is reasonable. Ensuring patient adherence to SGLT2i in addition to other HF therapy and lifestyle modification is also vital during patients' follow up.

Due to its glucosuric effect, SGLT2i increase the risk of genital mycotic infections by three-fold to four-fold in patients with diabetes. The vast majority of SGLT2i-related genital mycotic infections are treatable with topical antifungal agents or single oral fluconazole dose and do not necessitate discontinuation of SGLT2i therapy. Clinicians must counsel the patients regarding maintenance of genital hygiene. It is not clear if SGLT2i increase the risk of genital mycotic infections among

non-diabetic patients. Fournier's gangrene is a serious medical condition, and it remains uncertain whether SGLT2i increase its risk or not; however, it is worth noting that such an association has not been observed in any of the large SGLT2i trials. SGLT2is do not increase the risk of UTIs; however, their use in patients at high risk for UTIs, such as those with an indwelling Foley catheter, recurrent UTIs, and neurogenic bladder, has not been specifically studied.

## When and how should we initiate sodium-glucose cotransporter inhibitors in heart failure with reduced ejection fraction patients

Currently, ARNI, BB, MRA, and SGLT2i are considered the cornerstone of HFrEF therapy. SGLT2i qualified to become one of the foundational therapies that should be given to all patients with HFrEF and can be initiated at any step of treatment. The benefits of HFrEF therapies are additive/incremental, thus it is optimal to utilize all medication demonstrated to improve outcomes in combination, and start without delay so long as it is well-tolerated and not contraindicated. A dogmatically sequential or selective approach might lead to delays and endanger excess of HF hospitalization/deaths, which could have been prevented with earlier and more comprehensive implementation of GDMT.

## How should we consider the sequence of drugs in chronic heart failure with reduced ejection fraction

Initiation of the four pillars of HF disease-modifying therapies (ARNI/ACEI, beta-blockers, MRA, and SGLT2i) either simultaneously or sequentially within 4 weeks is currently recommended.<sup>38,39</sup> Regardless of the initiation sequence, the dose should be up-titrated to the maximum tolerated or target doses in a timely fashion (e.g. every 2 weeks).<sup>22</sup> This should be tailored according to the patient profiling—determined by BP, heart rate, presence of atrial fibrillation, chronic kidney disease, or hyperkalaemia.<sup>40</sup>

For beta-blockers to be initiated safely, physicians should ensure that patients are clinically euvoletic before the start of treatment to avoid worsening of HF. For symptomatic patients New York Heart Association class II–IV who satisfy eGFR criteria, it is recommended to add SGLT2 inhibitors to the initial therapy with ARNI/ACEI/ABR and beta-blockers (Figures 2 and 3).<sup>22</sup>

Treatment with MRAs can worsen renal function and produce hyperkalaemia; therefore, when starting MRAs, it seems advisable to have patients treated with a neprilysin inhibitor and a SGLT2 inhibitor, because these two drugs may mitigate the effect of spironolactone and eplerenone to worsen azotemia and increase serum potassium, and thereby, increase the likelihood that patients can be maintained on long-term MRA therapy. Once all four foundational drugs have been initiated within 4 weeks, physicians can then increase the dose of each drug towards the target doses used in clinical trials, as tolerated by the patient.<sup>41,42</sup>

Regardless of the specific approach, rapid sequencing has the potential to improve the adoption and effective implementation of treatments that reduce morbidity and mortality burdens in HFrEF.<sup>43</sup>

## Practical consideration

The use of SGLT2i in HFrEF carries vital considerations with respect to initiation in hospital admission, side effects, and adjustment with concomitant medications (Figure 4).

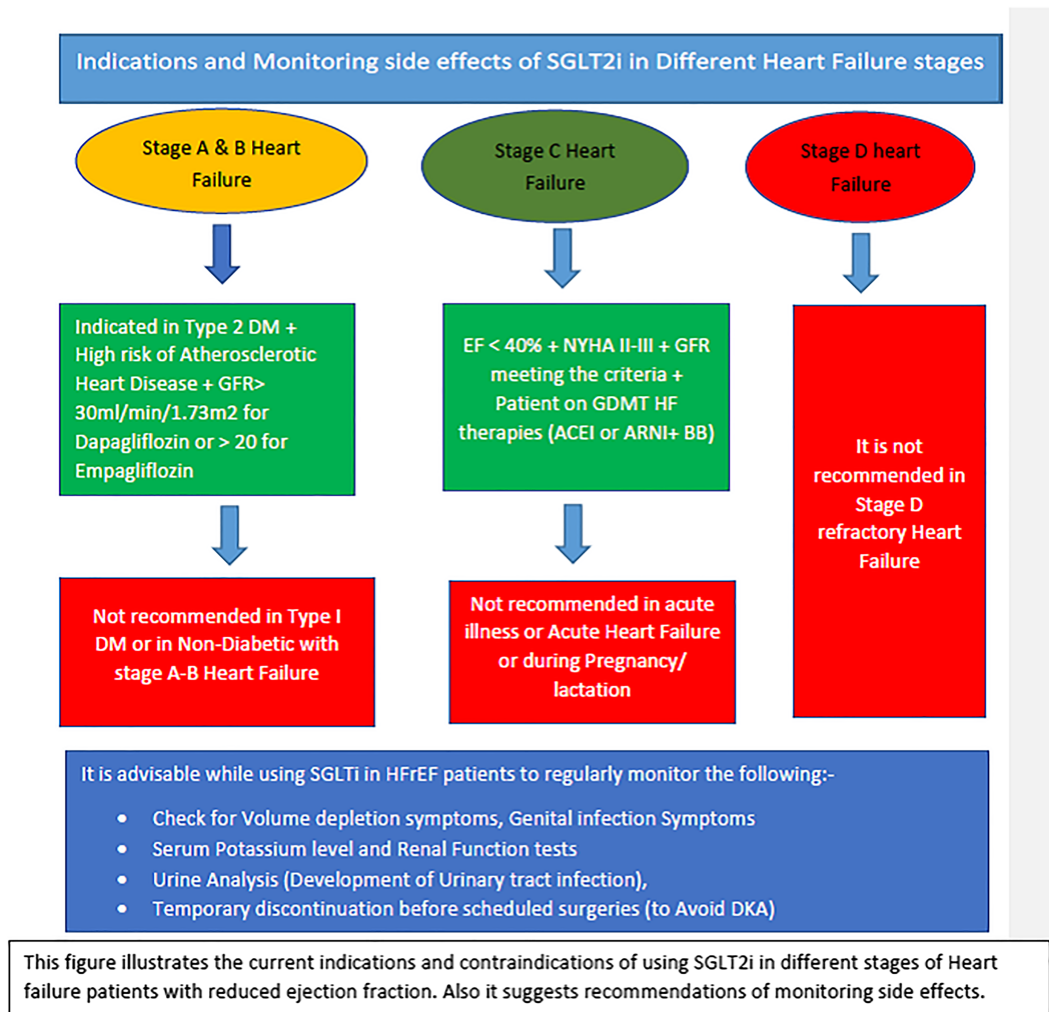
### 1. Initiation of SGLT2i in the hospital setting

There are promising data towards early initiation of SGLT2i after stabilization of acute condition and before hospital discharge. In DAPA-HF trial; patients early after hospitalization for HFrEF appeared to receive greater benefits from dapagliflozin. The EMPULSE trial, presented at the 2021 American Heart Association Scientific Sessions,<sup>44</sup> showed that empagliflozin was beneficial at reducing adverse events among patients with acute decompensated HF. The primary endpoint—a composite of death, number of HF events, time to first HF event, and change in Kansas City Cardiomyopathy Questionnaire-Total Symptom Score from baseline to 90 days—occurred at a rate of 53.9% in the empagliflozin group compared with 39.7% in the placebo group ( $P = 0.0054$ ) with no safety concerns with empagliflozin. However, the risk of diabetic keto acidosis should be considered in administering SGLT2i in acute ill patients.<sup>45</sup> To avoid delayed use of SGLT2i, the simultaneous or clustered drug initiation approach may improve patient compliance to guidelines directed therapies.<sup>43</sup>

### 2. Socio-economic consideration for using novel HF therapies

The economic burden of HF is booming specially with its progressively increasing prevalence, in addition to the high cost of many of novel therapies. In Egypt, the national health insurance is recently providing sacubitril/valsartan for insured patients. On the other hand, the out-of-pocket cost for uninsured patients receiving GDMT ranging be-

**Figure 2** Indications and monitoring of side effects of SGLT2i in different stages of HF. ACEI, angiotensin-converting enzyme inhibitor; ARNI, angiotensin receptor-neprilysin inhibitor; BB, beta-blockers; DKA, diabetic ketoacidosis; GDMT, guideline-directed medical therapy; GFR, glomerular filtration rate; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; NYHA, New York Heart Association; SGLT2i, sodium-glucose cotransporter inhibitor.



tween 700 and 2000 Egyptian Pounds per month, which might be unaffordable for a large sector of HFrEF patients. It is recommended to apply cost reduction measures whenever applicable such as using generic equivalent agents. Co-ordination of care between different medical specialties is another vital cost reductive strategy to avoid unnecessary duplication of investigations.

*Which comes first ARNI or SGLT2i?* As ARNI and SGLT2i drugs are relatively expensive compared with traditional HF therapies, the out-of-pocket costs together may not be affordable, given that sacubitril/valsartan carries a Class I guideline recommendation for patients with HFrEF; its preferential use could be considered.<sup>22</sup>

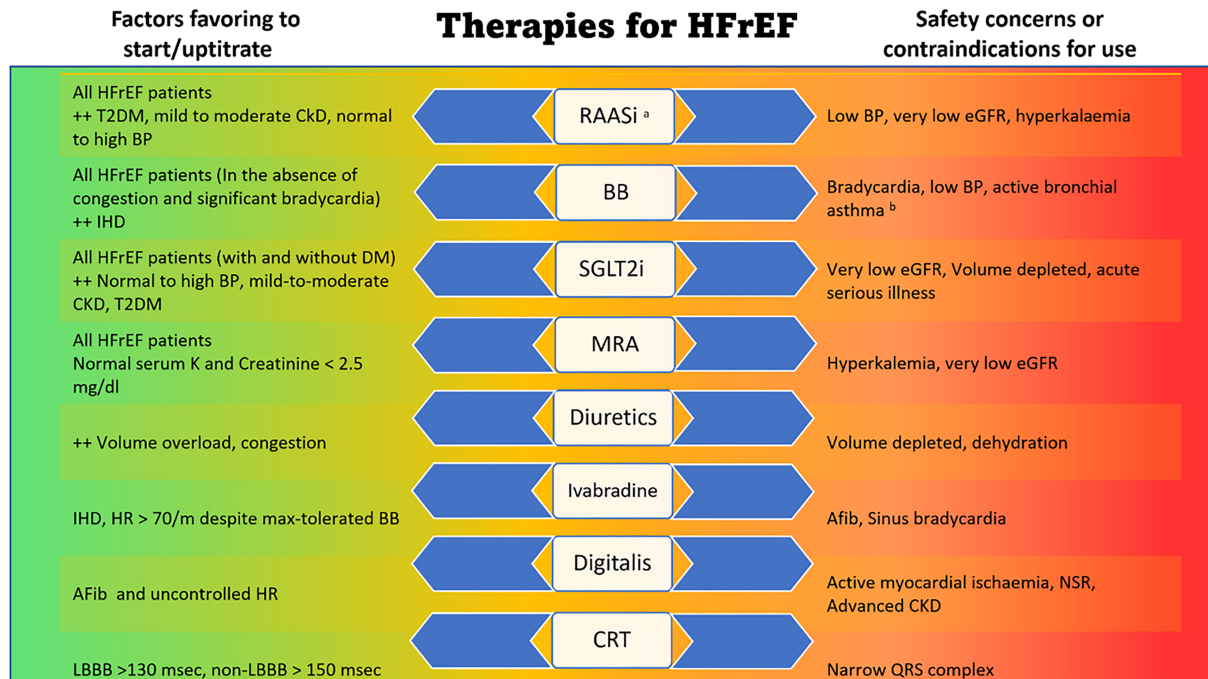
3. Patient with T2DM at risk for HF (Stages A & B HF); starting with metformin vs. SGLT2i?

Despite there are no clear recommendations for using SGLT2i in Stage A HF, patients with T2DM carries significant risk for developing HF. The usual practice in managing T2DM is to start with metformin, while SGLT2i come next. The recent ESC guidelines on CV disease protection and ESC guidelines for study of diabetes are currently advising SGLT2i as first-line T2DM therapy, in selected patients to reduce the risk of HF hospitalization.<sup>43,46</sup>

4. Adjustment with concomitant HF medications



**Figure 3** Choice of currently available therapies in patients with HFrEF.<sup>a</sup> ARNI are preferred over ACEI/ARBs if patient remained symptomatic.<sup>b</sup> Cardioselective BB (particularly nebivolol) can be started in small doses with caution, controlled COPD and stable bronchial asthma are not contraindications. ACEI, angiotensin-converting enzyme inhibitor; AFib, atrial fibrillation; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BB, beta-blockers; BP, blood pressure; CKD, chronic kidney disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid antagonists; RAASi, renin angiotensin aldosterone system inhibition, (encompassing ACEI, ARBs, and ARNI); SGLT2i, sodium-glucose cotransport type 2 inhibitors (dapagliflozin and empagliflozin).



Heart failure patients usually have several comorbidities that require long list of medications. Despite the wide safety margin of SGLT2i and limited drug interactions, its diuretic effect with risk volume depletion effect and risk of hyperkalaemia remain the main concerns specially when administered with other HF medications (loop diuretic, ARNI, and MRAs). Reducing the diuretic dose while using SGLT2i especially in old population is important to avoid significant dehydration and hypotension.

The risk of hyperkalaemia with SGLT2i is noted specially in patients in chronic kidney disease patients, and the risk is observed mainly with canagliflozin; however, the risk with other SGLT2i should be considered specially when given with other HF medications (ACEI, ARNI, and MRAs).<sup>43</sup>

We recommend regular monitoring of serum potassium especially in diabetic patients with CKD and on standard GDMT HF medical therapies.





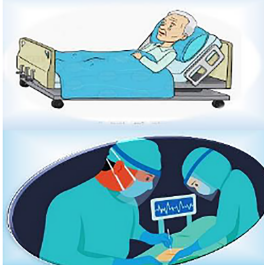

##### 5. Monitoring risks associated with SGLT2i

It is observed in several studies that SGLT2i are associated with common side effects especially with canagliflozin and

less side effects with dapagliflozin and empagliflozin. Close monitoring and follow up of these side effects are critical especially for the vulnerable HF patients.

- SGLT2i as a group is associated with increased risk of urinary tract infection UTI and genital mycotic infections. Regular monitoring of UTI symptoms and urine analysis is vital.
- Patient on SGLT2i with T2DM in acute illness carries an obvious risk of ketoacidosis. It is advisable avoid dehydration and to stop SGLT2i in acute illness and to hold it 3 days prior to scheduled surgeries to avoid such risk.<sup>47</sup>
- Symptomatic hypotension is a notable side effect especially in HF patients taking other antifailure medications that lower BP. Careful monitoring of fluid status and dose adjustment of HF medications are essential
- Canagliflozin is associated with increased risk of bone fracture as observed in CANVAS trial. It is suggested to be cautious while using canagliflozin in old patients liable for osteoporosis. The FDA removed boxed warning about the risk of leg and foot amputations in patients using canagliflozin.<sup>47</sup>

**Figure 4** Practical considerations for the use of SGLT2i. eGFR, estimated glomerular filtration rate; SGLT2i, sodium-glucose cotransport type 2 inhibitors.

<b>Practical considerations for the use of SGLT2i</b>	
<p><b>A. <u>PATIENT SCREENING AND EDUCATION</u></b></p> <ul style="list-style-type: none"> <li>➤ Appropriate patient selection</li> <li>➤ Discussing benefits and concerns of the drug</li> <li>➤ Educate about Sx of possible side effects</li> </ul>	
<p><b>B. <u>ASSESSMENT OF IMPORTANT VARIABLES</u></b></p> <ul style="list-style-type: none"> <li>➤ Blood pressure</li> <li>➤ Kidney functions (baseline eGFR)</li> <li>➤ Glycaemic status</li> </ul>	
<p><b>C. <u>REVISE AND ADJUST BACKGROUND THERAPY</u></b></p> <ul style="list-style-type: none"> <li>➤ Consider reduce diuretics for euvolemic patients</li> <li>➤ Avoid combination of SGLT2-i + metformin + long-acting sulfonyl urea</li> </ul>	
<p><b>D. <u>INSTRUCT TO AVOID DEHYDRATION</u></b></p> <ul style="list-style-type: none"> <li>➤ Educate on importance of appropriate water intake</li> </ul>	
<p><b>E. <u>CONSIDER TRANSIENT DISCONTINUATION DURING ACUTE ILLNESS OR PRIOR TO SURGERIES</u></b></p> <ul style="list-style-type: none"> <li>➤ To minimize risk of euglycaemic ketoacidosis in high-stress conditions</li> </ul>	
<p><b>F. <u>INTENSIFY ON TOILET AND GENITO-URINARY HYGIENE</u></b></p> <ul style="list-style-type: none"> <li>➤ To minimize risk of genito-urinary infections</li> </ul>	

## References

1. Jagannathan R, Patel SA, Ali MK, Narayan KMV. Global updates on cardiovascular disease mortality trends and attribution of traditional risk factors. *Curr Diab Rep* 2019; **19**: 44.
2. van Riet EES, Hoes AW, Wagenaar KP, Limburg A, Landman MAJ, Rutten FH. Epidemiology of heart failure: the prevalence of heart failure and ventricular dysfunction in older adults over time. A systematic review. *Eur J Heart Fail* 2016; **18**: 242–252.
3. Dei Cas A, Fonarow GC, Gheorghide M, Butler J. Concomitant diabetes mellitus and heart failure. *Curr Probl Cardiol* 2015; **40**: 7–43.
4. Kannel WB. Diabetes and cardiovascular disease. *JAMA* 1979; **241**: 2035.
5. Timmis A, Townsend N, Gale C, Grobbee R, Maniadakis N, Flather M, Wilkins E, Wright L, Vos R, Bax J, Blum M. ESC sci-

- entific document group. European Society of Cardiology: cardiovascular disease statistics 2017. *Eur Heart J* 2018; **39**: 508–579.
6. Ogurtsova K, da Rocha Fernandes JD, Huang Y, Linnenkamp U, Guariguata L, Cho NH, Cavan D, Shaw JE & Makaroff LE. IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. *Diabetes Res Clin Pract* 2017; **128**: 40–50.
  7. Hassanein M, Abdelhamid M, Ibrahim B, Elshazly A, Aboleineen MW, Sobhy H, Nasr G, Elmesseyry F, Abdelmoneim A, Ashmawy M, Farag N, Youssef A, Elbahry A, Elrakshy Y, Sobhy M, Khairy Abdel Dayem TM, Ebeid H, Reda A, Boshra H, Saleh A, Maggioni AP. Clinical characteristics and management of hospitalized and ambulatory patients with heart failure—results from ESC heart failure long-term registry-Egyptian cohort. *ESC Hear Fail* 2015; **2**: 159–167.
  8. Hassanein M, Abdelhamid M, Ibrahim B, Sobhy M, Nasr G, Aboleineen MW, Reda A, Farag N, Elshazly A, Abdeldayem TK, Elmesseyry F, Boshra H, Sobhy H, Elbahry A, Youssef A, Ashmawy M, Abdelmoneim A, Saleh A, Elrakshy Y, Ebeid H. Gender differences in Egyptian patients hospitalized with heart failure: insights from the European Society of Cardiology Heart Failure Long-Term Registry. *ESC Hear Fail* 2018; **5**: 1159–1164.
  9. Ferro EG, Michos ED, Bhatt DL, Lincoff AM, Elshazly MB. New decade, new FDA guidance for diabetes drug development. *J Am Coll Cardiol* 2020; **76**: 2522–2526.
  10. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 2007; **356**: 2457–2471.
  11. Cosmi F, Shen L, Magnoli M, Abraham WT, Anand IS, Cleland JG, Cohn JN, Cosmi D, de Berardis G, Dickstein K, Franzosi MG, Gullestad L, Jhund PS, Kjekshus J, Køber L, Lepore V, Lucisano G, Maggioni AP, Masson S, McMurray JJV, Nicolucci A, Petrarolo V, Robusto F, Staszewsky L, Tavazzi L, Teli R, Tognoni G, Wikstrand J, Latini R. Treatment with insulin is associated with worse outcome in patients with chronic heart failure and diabetes. *Eur J Heart Fail* 2018; **20**: 888–895.
  12. Scirica BM, Braunwald E, Raz I, Cavender MA, Morrow DA, Jarolim P, Udell JA, Mosenzon O, Im K, Umez-Eronini AA, Pollack PS, Hirshberg B, Frederich R, Lewis BS, McGuire D, Davidson J, Steg PG, Bhatt DL, SAVOR-TIMI 53 Steering Committee and Investigators\*. Heart failure, saxagliptin, and diabetes mellitus: observation from the SAVOR-TIMI 53 randomized trial. *Circulation* 2014; **130**: 1579–1588.
  13. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015; **373**: 2117–2128.
  14. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Ruff CT, Gause-Nilsson IAM, Fredriksson M, Johansson PA, Langkilde AM, Sabatine MS. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019; **380**: 347–357.
  15. Kluger AY, Tecson KM, Barbin CM, Lee AY, Lerma EV, Rosol ZP, Rangaswami J, Lepor NE, Cobble ME, McCullough PA. Cardiorenal outcomes in the CANVAS, DECLARE-TIMI 58, and EMPA-REG OUTCOME trials: a systematic review. *Rev Cardiovasc Med* 2018; **19**: 41–49.
  16. Rosano GM, Moura B, Metra M, Bauersachs J, Gal TB, Adamopoulos S, Abdelhamid M, Bistola V, Bohm M, Celutkien J, Chioncel O, Farmakis D, Ferrari R, Filippatos G, Hill L, Jankowska EA, Jaarsma T, Jhund P, Lainscak M, Lopatin Y, Lund LH, Milicic D, Mullens W, Pinto F, Ponikowski P, Savarese G, Thum T, Volterrani M, Anker SD, Seferovic PM, Coats AJS. Patient profiling in heart failure for tailoring medical therapy. A consensus document of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2021; **6**: 872–881.
  17. Neal B, Perkovic V, Mahaffey KW, De Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017; **377**: 644–657.
  18. McMurray JJ, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Bělohávek J, Böhm M. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019; **381**: 1995–2008.
  19. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, Januzzi J, Verma S, Tsutsui H, Brueckmann M, Jamal W, Kimura K, Schnee J, Zeller C, Cotton D, Bocchi E, Böhm M, Choi DJ, Chopra V, Chuquiure E, Giannetti N, Janssens S, Zhang J, Gonzalez Juanatey JR, Kaul S, Brunner-la Rocca HP, Merkely B, Nicholls SJ, Perrone S, Pina I, Ponikowski P, Sattar N, Senni M, Seronde MF, Spinar J, Squire I, Taddei S, Wanner C, Zannad F. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med* 2020; **383**: 1413–1424.
  20. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola V-P, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. Authors/Task Force Members, Document Reviewers. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016; **18**: 891–975.
  21. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stev S. 2016 ACC/AHA/HFSA focused update on new pharmacological therapy for heart failure: an update of the 2013 ACCF/AHA guideline for the management of heart failure. *Circulation* 2016; **134**: e282–e293.
  22. Maddox TM, Januzzi JL Jr, Allen LA, Breathett K, Butler J, Davis LL, Fonarow GC, Ibrahim NE, Jessup M, Lindenfeld J, Maddox TM, Masoudi FA. 2021 update to the 2017 ACC expert consensus decision pathway for optimization of heart failure treatment: answers to 10 pivotal issues about heart failure with reduced ejection. *J Am Coll Cardiol* 2021; **77**: 772–810.
  23. Lam C, Chandramouli C, Ahojva V, Verma S. SGLT-2 inhibitors in heart failure: current management, unmet needs, and therapeutic prospects. *J Am Heart Assoc* 2019; **8**: e013389.
  24. Kaur N, Pruthvi C, Rohit M. Will introduction of ARNI reduce the need of device therapy in heart failure with reduced ejection fraction? *Egyptian Heart J* 2021; **73**: 26.
  25. Joshi SS, Singh T, Newby DE, Singh J. Sodium glucose co-transporter 2 inhibitor therapy: mechanisms of action in heart failure. *World J Diabetes* 2020; **11**: 269–279.
  26. Inzucchi SE, Kosiborod M, Fitchett D, Wanner C, Hehnke U, Kaspers S, George JT, Zinman B. Improvement in cardiovascular outcomes with empagliflozin is independent of glycemic control. *Circulation* 2018; **138**: 1904–1907.
  27. Zannad F, Ferreira JP, Pocock SJ, Anker SD, Butler J, Filippatos G, Brueckmann M, Ofstad AP, Pfarr E, Jamal W, Packer M. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-reduced and DAPA-HF trials. *Lancet* 2020; **6736**: 1–11.
  28. Januzzi J, Ferreira JP, Böhm M, Kaul S, Wanner C, Brueckmann M, Petrie MC, Ofstad AP, Zeller C, George J, Fitchett D, Zannad F. Empagliflozin reduces the risk of a broad spectrum of heart failure outcomes regardless of heart failure status at baseline. *Eur J Heart Fail* 2019; **21**: 386–388.
  29. Butler J, Usman MS, Khan MS, Greene SJ, Friede T, Vaduganathan M, Filippatos G, Coats AJS, Anker SD. Efficacy and safety of SGLT 2 inhibitors in heart failure: systematic review and meta-analysis. *ESC Hear Fail* 2020; **7**: 3298–3309.

30. McCoy RG, Dykhoff HJ, Sangaralingham L, Ross JS, Karaca-Mandic P, Montori VM, Shah ND. Adoption of new glucose-lowering medications in the US—the case of SGLT2 inhibitors: nationwide cohort study. *Diabetes Technol Ther* 2019; **21**: 702–712.
31. Perkovic V, Jardine M, Neal B, Bompoint S, Heerspink H, Charytan D, Edwards R, Rajiv A, Bakris G, Bull S, Cannon C, Capuano G, Chu P, Zeeuw D, Greene T, Levin A, Pollock C, Wheeler D, Yavin Y, Zhang H, Zinman B, Meininger G, Brenner B, Mahaffey K. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019; **380**: 2295–2306.
32. Heerspink HJ, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou F-F, Mann JF, McMurray JJ, Lindberg M, Rossing P, Sjöström CD. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med* 2020; **383**: 1436–1446.
33. Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA, DeFronzo RA, Garber JR, Garvey WT. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm. *Endocr Pract Off J Am Coll Endocrinol Am Assoc Clin Endocrinol* 2020; **26**: 107–139.
34. Jorsal A, Persson F, Bruun JM. Comments on the 2019 ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases. *Eur Heart J* 2020; **41**: 328.
35. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, Federici M, Filippatos G, Grobbee DE, Hansen TB, Huikuri HV, Johansson I, Jüni P, Lettino M, Marx N, Mellbin LG, Östgren CJ, Rocca B, Roffi M, Sattar N, Seferović PM, Sousa-Uva M, Valensi P, Wheeler DC, ESC Scientific Document Group. 2019 ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the task force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD). *Eur Heart J* 2020; **41**: 255–323.
36. Vardeny O, Vaduganathan M. Practical guide to prescribing sodium-glucose cotransporter 2 inhibitors for cardiologists. *JACC: Heart Fail* 2019; **7**: 169–172.
37. Neuen BL, Young T, Heerspink HJ, Neal B, Perkovic V, Billot L, Mahaffey KW, Charytan DM, Wheeler DC, Arnott C, Bompoint S. SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol* 2019; **7**: 845–854.
38. Vaduganathan M, Claggett BL, Jhund PS, Cunningham JW, Pedro Ferreira J, Zannad F, Packer M, Fonarow GC, McMurray JJV, Solomon SD. Articles estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials. *Lancet* 2020; **6736**: 1–8.
39. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumhach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, Cleland JG. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2021; **42**: 3599–3726.
40. Rosano GMC, Moura B, Metra M, Bauersachs J, Gal TB, Adamopoulos S, Abdelhamid M, Bistola V, Bohm M, Čelutkienė J, Chioncel O. Patient profiling in heart failure for tailoring medical therapy. A consensus document of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2021; **23**: 872–881.
41. McMurray JJ, Packer M. How should we sequence the treatments for heart failure and a reduced ejection fraction. *Circulation* 2021; **143**: 875–877.
42. Greene SJ, Butler J, Fonarow GC. Simultaneous or rapid sequence initiation of quadruple medical therapy for heart failure—optimizing therapy with the need for speed. *JAMA Cardiol* 2021.
43. Honigberg MC, Vardeny O, Vaduganathan M. Practical considerations for the use of sodium-glucose cotransporter 2 inhibitors in heart failure. *Circ Heart Fail* 2020; **13**: e006623.
44. Voors AA, Angermann CE, Teerlink JR, Zieroth S, for the EMPULSE Trial Investigators. Empagliflozin in patients hospitalized for acute heart failure: the EMPULSE trial. Presented at the 2021 American Heart Association Scientific Sessions, Virtual; November 14.
45. Tamaki S, Yamada T, Watanabe T, Morita T, Furukawa Y, Kawasaki M, Kikuchi A, Kawai T, Seo M, Abe M, Nakamura J. Effect of empagliflozin as an add-on therapy on decongestion and renal function in patients with diabetes hospitalized for acute decompensated heart failure: a prospective randomized. *Circ Heart Fail* 2021; **14**: e007048.
46. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Böck M, Benetos A, Biffi A, Boavida J-M, Capodanno D, Cosyns B, Crawford C, Davos CH, Desormais I, di Angelantonio E, Franco OH, Halvorsen S, Hobbs FDR, Hollander M, Jankowska EA, Michal M, Sacco S, Sattar N, Tokgozoglul, Tonstad S, Tsioufis KP, van Dis I, van Gelder IC, Wannan C, Williams B, ESC Scientific Document Group, de Backer G, Regitz-Zagrosek V, Aamodt AH, Abdelhamid M, Aboyans V, Albus C, Asteggiano R, Böck M, Borger MA, Brotons C, Čelutkienė J, Cifkova R, Cikes M, Cosentino F, Dagres N, de Backer T, de Bacquer D, Delgado V, den Ruijter H, Dendale P, Drexel H, Falk V, Fauchier L, Ference BA, Ferrières J, Ferrini M, Fisher M, Fliser D, Fras Z, Gaita D, Giampaoli S, Gielen S, Graham I, Jennings C, Jorgensen T, Kautzky-Willer A, Kavousi M, Koenig W, Konradi A, Kotecha D, Landmesser U, Lettino M, Lewis BS, Linhart A, Løchen M-L, Makrillakis K, Mancia G, Marques-Vidal P, McEvoy JW, McGreevy P, Merkely B, Neubeck L, Nielsen JC, Perk J, Petersen SE, Petronio AS, Piepoli M, Pogosova NG, Prescott EIB, Ray KK, Reiner Z, Richter DJ, Rydén L, Shlyakhto E, Sitges M, Sousa-Uva M, Sudano I, Tiberi M, Touyz RM, Ungar A, Verschuren WMM, Wiklund O, Wood D, Zamorano JL, Smulders YM, Carballo D, Koskinas KC, Böck M, Benetos A, Biffi A, Boavida J-M, Capodanno D, Cosyns B, Crawford CA, Davos CH, Desormais I, di Angelantonio E, Franco Duran OH, Halvorsen S, Richard Hobbs FD, Hollander M, Jankowska EA, Michal M, Sacco S, Sattar N, Tokgozoglul, Tonstad S, Tsioufis KP, Dis I v, van Gelder IC, Wannan C, Williams B. 2021 ESC guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2021; **42**: 3227–3337.
47. Faulkenberg KD, Williams JB, Isaacs DM, West LM. Practical considerations and opportunities for SGLT2 inhibitor prescription in heart failure. *Curr Treat Options Cardiovasc Med* 2020; **22**: 1–15.