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Review

The Safety and Efficacy of Sodium-Glucose Cotransporter-2 Inhibitors for Patients with Sarcopenia or Frailty: Double Edged Sword?

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Abstract: Sodium-glucose cotransporter-2 inhibitors (SGLT-2is) show cardiovascular protective effects, regardless of the patient's history of diabetes mellitus (DM). SGLT2is suppressed cardiovascular adverse events in patients with type 2 DM, and furthermore, SGLT-2is reduced the risk of worsening heart failure (HF) events or cardiovascular death in patients with HF. Along with these research findings, SGLT-2is are recommended for patients with HF in the latest guidelines. Despite these benefits, the concern surrounding the increasing risk of body weight loss and other adverse events has not yet been resolved, especially for patients with sarcopenia or frailty. The DAPA-HF and DELIVER trials consistently showed the efficacy and safety of SGLT-2i for HF patients with frailty. However, the Rockwood frailty index that derived from a cumulative deficit model was employed for frailty assessment in these trials, which might not be suitable for the evaluation of physical frailty or sarcopenia alone. There is no fixed consensus on which evaluation tool to use or its cutoff value for the diagnosis and assessment of frailty in HF patients, or which patients can receive SGLT-2i safely. In this review, we summarize the methodology of frailty assessment and discuss the efficacy and safety of SGLT-2i for HF patients with sarcopenia or frailty.

Keywords: sodium-glucose cotransporter-2 (SGLT-2) inhibitors; heart failure; frailty; sarcopenia

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1. Introduction

Sodium-glucose cotransporter-2 inhibitors (SGLT-2is) are drugs that increase urinary sodium and glucose excretion by inhibiting the effect of SGLT-2 in the proximal renal tubules [1]. Accumulating evidence suggests that SGLT-2is show not only blood-glucose-lowering effects but also cardiovascular protective effects. The various mechanisms mediating its beneficial effect [2] include the diuretic effect by sodium discharge and osmotic diuresis [3,4], glomerular and tubular protection [5], increased erythropoiesis [3,6,7], sympathetic nervous system inhibition [8,9], improvement of myocardial energy metabolism [10,11], suppression of chronic inflammation [12] or oxidative stress [11], and weight reduction [13]. In large-scale randomized control trials such as EMPA-REG OUTCOME, CANVAS program, and DECLARE–TIMI 58, SGLT-2is, including empagliflozin, canagliflozin and dapagliflozin suppressed the composite outcome of cardiovascular death, nonfatal myocardial infarction, and stroke for the patients with type 2 diabetes mellitus (DM) and high risk of cardiovascular events (Table 1) [14–16]. As a result, the exploration of SGLT-2is' beneficial effect was extended to the heart failure (HF) population. In the EMPEROR-Reduced and DAPA-HF trial [17,18], the risk of worsening HF events (hospitalization or urgent visit resulting in intravenous therapy for HF) or cardiovascular death

were suppressed in the patients with heart failure and reduced ejection fraction (HFrEF) who received SGLT-2is compared to those who received a placebo. This beneficial effect of SGLT-2is on HFrEF patients has been observed regardless of the history of DM [18,19]. Furthermore, SGLT-2is successfully improved the clinical outcome even in patients with HF and preserved EF (HFpEF), although there had been no agents that demonstrated the prognostic benefit in this population until then [20,21]. In addition, SGLT-2is consistently provide evidence of HF event reduction in these studies, although the mortality benefit has been controversial [17–21]. Further, the treatment effect of SGLT-2is was not significantly influenced by EF [22]. Along with these research findings, SGLT-2is are recommended for patients with HF irrespective of EF in the AHA/ACC/HFSA guidelines [23] and ESC guidelines [24]. Despite these benefits, the concern surrounding the increasing risk of body weight loss, urogenital infection, hypoglycemia, volume depletion, bone fracture, and diabetic ketoacidosis has not yet been resolved [25]. Further, there have been significant concerns surrounding these adverse effects for elderly populations because of the increased susceptibility to side effects, impaired awareness of adverse events, poorer adherence and higher risk of falling. Among these adverse effects, weight loss and bone fracture might be derived from renal glucose excretion and energy loss by inhibiting SGLT-2. Thus, the safety of SGLT-2is in frail patients is still unclear.

Table 1. The landmark trials that assessed the safety and efficacy of SGLT-2is and their main findings.

Population	SGLT-2is	Trial	Primary Endpoint
T2DM and high risk of CVD	Empagliflozin	EMPA-REG OUTCOME [14]	MACE, HR 0.86 [95%CI, 0.74–0.99]
	Canagliflozin	CANVAS program [15]	MACE, HR 0.86 [95%CI, 0.75–0.97]
	Dapagliflozin	DECLARE-TIIM 58 [16]	The composite of CV death and hospitalization for HF, HR 0.83 [95%CI, 0.73–0.95]
HFrEF	Empagliflozin	EMPEROR-Reduced [18]	The composite of CV death and hospitalization for HF, HR 0.75 [95%CI, 0.65–0.86]
	Dapagliflozin	DAPA-HF [17]	The composite of CV death and hospitalization or urgent intravenous therapy for HF, HR 0.74 [95%CI, 0.65–0.85]
T2DM and HF	Sotagliflozin	SOLOIST-WHF [19]	The composite of CV death and hospitalization or urgent visit for HF, HR 0.67 [95%CI, 0.52–0.85]
HFpEF	Dapagliflozin	DELIVER [20]	The composite of CV death and hospitalization for HF, HR 0.82 [95%CI, 0.73–0.92]
	Empagliflozin	EMPEROR-Preserved [21]	The composite of CV death and hospitalization for HF, HR 0.79 [95%CI, 0.69–0.90]
Acute HF	Empagliflozin	EMPULSE [26]	The composite of all-cause death, worsening HF event, and KCCQ-TSS, stratified win ratio 1.36 [95%CI, 1.09–1.68]

HR, hazard ratio; CI, confidence interval; T2DM, type 2 diabetes mellitus; CVD, cardiovascular disease; MACE, major advanced cardiovascular events (defined as the composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke); HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; KCCQ-TSS, The Kansas City Cardiomyopathy Questionnaire Total Symptom Score; EMPA-REG, The Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose; CANVAS, Canagliflozin Cardiovascular Assessment Study; DECLARE-TIMI, The Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction; EMPEROR-Reduced, The Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and Reduced Ejection Fraction; DAPA-HF, Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; DELIVER, Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure; SOLIST-WHF, the Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure; DELIVER, The Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure; EMPEROR-Preserved, The Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection

Fraction; EMPULSE, Empagliflozin in Patients Hospitalized With Acute Heart Failure Who Have Been Stabilized.

The presence of frailty [27–32] or sarcopenia [33–37] is known as a prognostic aggravating factor in HF, leading to a higher risk of hospitalization and mortality. According to the remarkably accelerated aging of HF populations [38], the prevalence of frailty or sarcopenia has been dramatically increasing and is further expected to keep rising in the future [39]. Aging is the most significant contributing factor to frailty and these are deeply related to each other but not necessarily parallel. In addition, although there are scales widely used to assess frailty (Table 2), no scale has been established specifically for HF patients.

Table 2. The main tools for the assessment of frailty or sarcopenia.

Frailty or Sarcopenia	Assessment	Measure	Description
Sarcopenia	Muscle mass	Skeletal muscle mass index (SMI) (appendicular skeletal muscle mass/height^2)	Various cutoffs employed by studies
	Muscle strength	Hand grip	Various cutoffs employed by studies
Sarcopenia/Frailty	Physical function	Gait speed	
	Physical function	Short Physical Performance Battery (SPPB) [40]	A summation of scores on three tests: balance, gait speed and chair stand
	Physical function	Timed-Up and Go test (TUG) [41]	
Frailty	Multidimensional	Rockwood frailty index [42]	Accumulation of symptoms, function, comorbidities, clinical laboratory abnormalities, and impaired quality of life are assessed using 93 variables
	Phenotype model	Barthel index [43]	Score is calculated based on several daily activities (feeding, bathing, grooming, dressing, bowel and bladder control, toilet use capability, transfer from bed to chair and vice-versa, mobility on level surfaces, and capability to climb stairs)
	Medical domain	Clinical frailty scale [44]	A semi-quantitative global judgement
	Medical domain and physical function	Fried frailty phenotype [45]	Weight loss, weakness of hand grip, exhaustion, slowness, and low activity

According to the American Diabetes Association Guideline recommendation [46], management of elderly DM patients requires individualized treatment targets that take account of their comorbidities because of the risk of hypoglycemia or ketosis resulting from the disruption of diet and medication. With the aforementioned risks, some trials indicate that SGLT-2is administration for elderly patients has similar or greater benefits for cardiovascular or renal function than younger patients [46]. Nevertheless, it is necessary to consider the characteristics of each racial group for worldwide consensus, especially Asian populations that have differences in body composition and cardiometabolic risk from Caucasian populations [47].

Hence, in this review, we summarize the methodology of frailty assessment and discuss the efficacy and safety of SGLT-2is for HF patients with frailty.

2. Definition and Etiology of Sarcopenia or Frailty

Sarcopenia and frailty are sometimes associated with a similar clinical picture but these two terms differ substantially in terms of their concept. Sarcopenia is a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life and death [48,49]. According to the conceptual definition of sarcopenia by the European Working Group on Sarcopenia in Older People (EWGSOP), diagnosis of sarcopenia is made by the presence of both low muscle mass and low muscle function such as muscle strength or physical performance [50,51]. Further, it is defined as severe sarcopenia when all of these three components (low muscle mass, low strength and low physical performance) are present [50,51]. By the current recommendation, the assessment tool for sarcopenia is composed of muscle mass measured by Appendicular Skeletal Muscle Mass (ASM), muscle strength measured by grip or chair stand, and physical performance measured by gait speed, Short Physical Performance Battery (SPPB) [40], or Timed-Up and Go test (TUG) (Table 2) [41,51]. This recommendation focuses on European populations, while different diagnostic criteria have been proposed for Asian populations by the Asian Working Group for Sarcopenia (AWGS) [52], since body composition substantially differs between these ethnicities [47].

On the other hand, frailty is classically defined as the presence of three or more of the following criteria: unintentional weight loss (more than 4.5 kg in 1 year), slow gait speed, weak grip strength and self-reported physical exhaustion or measured low physical activity [45]. However, the concept of frailty has been broadened and is now defined as the deterioration of multidimensional and multisystem conditions characterized by decreased functional reserves and increased vulnerability to stress and acute adverse events [53]. Thus, it is a broad concept in contrast to sarcopenia, which focuses on muscle mass or weakness. Frailty includes a medical domain, a physical domain, a cognitive/depressive status domain, and a social domain [54]. Although there are various indices and scores proposed to quantify frailty which is the complex multisystem condition, there are two basic concepts of frailty, phenotype model and the cumulative deficit model [55]. The phenotype model is a measure of the presence of symptoms or physical functions such as activity of daily living (ADL), which includes the Barthel index [43], clinical frailty scale [44], and Fried frailty phenotype defined by weight loss, weakness of hand grip, exhaustion, slowness, and low activity (Table 2) [45]. The cumulative deficit model, on the other hand, is a measure of the accumulation of symptoms, function, comorbidities, clinical laboratory abnormalities, and questionnaire of quality of life, which is represented by the Rockwood frailty index using 93 variables (Table 2) [42]. Although various scales have been used in recent HF studies, the following scales are commonly used: Fried frailty phenotype, Rockwood frailty index, Barthel index, and clinical frailty scale [56]. The Rockwood frailty index has recently been adopted as an evaluation scale for frailty in DAPA-HF [57] and DELIVER trials [58], both of which showed the efficacy of SGLT-2is for HF patients with frailty, and these attracted much attention. However, there is no fixed consensus on the cutoff value for these frailty diagnostic scales.

It should not be forgotten that there is regional variability in the prevalence of frailty. A recent meta-analysis reported that the prevalence of frailty in an Asian population aged over 60 years was 20.5% [59], which was roughly equal to those reported in Latin American and Caribbean populations [60], but higher than in European, North American, and Oceanian populations [61–63]. However, due to the lack of a uniform evaluation scale, we need to be cautious to interpret these data of regional differences, suggesting the difficulty of making an unbiased regional comparison and development of a global countermeasure against this issue.

3. Heart Failure and Frailty/Sarcopenia

Body weight loss in HF patients was called "cardiac cachexia" especially with a change in body composition [64]. Cachexia is a concept that includes skeletal muscle wasting, anemia, anorexia, and altered immune function, which results in fatigue, impaired quality of life, and an aggregate prognosis [65], and it can occur in patients with a variety of diseases such as HF, chronic obstructive pulmonary disease, renal failure, and cancer. It is different from sarcopenia in terms of its concept, which is not limited to muscle weakness [64]. In HF patients, dyspnea, fatigue, and anorexia can lead to a low nutritional state and reduction in physical activity, which leads to sarcopenia, and further weakening of muscle or physical function. This vicious circle is called the "frailty cycle" [66] (Figure 1).

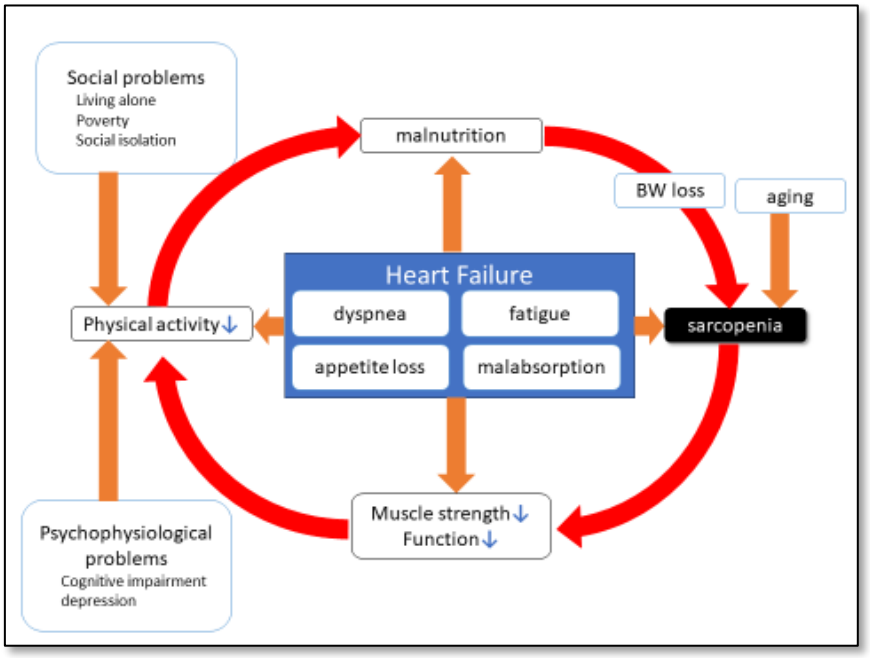

Figure 1. Frailty cycle in HF. Malnutrition can cause body weight loss and muscle loss (sarcopenia), accompanied by deteriorated muscle strength and function, which results in depressed physical activity. As a result, the decrease in oral intake induces further malnutrition. This vicious cycle is often referred to as the frailty cycle. In the setting of HF, the symptoms include dyspnea, fatigue, appetite loss and intestinal malabsorption due to intestinal congestion and malperfusion. These symptoms can accelerate every single step in the frailty cycle. Further, elderly populations are commonly affected by HF and have various problems that further accelerate the frailty cycle. Red arrows indicate the main pathway of the frailty cycle. Orange arrows indicate the aggravation of each component. ↓, decrease. BW, body weight; HF, heart failure.

It is well known that sarcopenia and frailty are strongly associated with a poor prognosis in HF patients. HF patients have a higher prevalence of sarcopenia (by ~20%) compared to healthy subjects of the same age and it is associated with worse clinical outcomes independently [67]. Frailty is prevalent in HF patients, representing 40-80% of overall HF, 30-60% of HF with a reduced ejection fraction (HFrEF), and up to 90% of HF with a preserved ejection fraction (HFpEF) [68–73]. In the FRAIL-HF study, HF patients with frailty showed a higher prevalence of depression, worse score of health literacy, few HF medications, and higher risk of mortality and rehospitalization [74]. A recent meta-analysis reported that the presence of frailty in chronic HF is associated with an increased risk of death and hospitalization by approximately 1.5-fold [75]. The reasons why frailty is associated with a worse prognosis are related to HF aggravation by comorbidities such as anemia and renal dysfunction, muscle weakness leading to increased cardiac load [76], diffi-

culty in initiating medications due to organ dysfunction or fall risk by drug-induced hypotension or dehydration, and lower adherence to medication because of cognitive or social frailty.

In addition, in the late 20th century, a subset of older adults was identified as having both obesity and sarcopenia, soon thereafter termed as "sarcopenic obesity". Sarcopenic obesity is defined by excess adiposity with a loss of muscle mass and/or function [77]. Aging is a systemic process affecting all organ systems and associated with significant alterations in body composition. Typically, fat mass increases with age [78], whereas muscle mass and strength start to decline progressively [79]. While aging is associated with a systemic pro-inflammatory state, oxidative stress, and altered endocrine function leading to the loss of muscles [80], obesity has multiple adverse consequences for skeletal muscle, including inflammation, oxidative stress, and insulin resistance. Along with visceral fat accumulation, loss of skeletal muscle, which is the largest insulin-responsive target tissue, produces insulin resistance. Adding to this, increases in visceral fat may lead to a higher secretion of pro-inflammatory adipokines that further promote insulin resistance as well as potentially direct catabolic effects on muscles [81,82]. The reports on the epidemiology of sarcopenic obesity are limited, but in a 14-year prospective study of the elderly population in the United States, its prevalence was 19–34% in women and 13–27% in men [83]. In the HF population, the prevalence of sarcopenic obesity was reported to be 4.0–18.5% [33,84]. Coexistence of sarcopenic obesity is a predictor of disability and mortality [85,86], and associated with a reduction in cardiorespiratory fitness independent of adiposity [87]. However, the data on its pathophysiology and prognostic impact compared to lean sarcopenia are needed.

4. Safety and Efficacy of SGLT-2is for Sarcopenic or Frail Patients

The hypothetical mechanisms mediating the efficacy of SGLT-2is for HF patients are the following: cardio–renal coupling, ketone production, diuretic effect, hematopoietic effect, direct prevention of myocardial remodeling, and suppression of neurohumoral factor [2], and it is considered that each of them have interrelated effects. Since many studies have recently reported the efficacy of SGLT-2is for HF regardless of the history of DM [18,19], their efficacy seems to be not only related to the blood-glucose-lowering effect. Further, the beneficial effect was observed regardless of left ventricular EF [14,19–21,88–91]. Some randomized controlled studies have carried out sub-analysis that focused on frailty (Table 3). In the DELIVER trial, the presence or severity of frailty was assessed for 6258 study patients by their frailty index (FI) at baseline and they were divided into four classes by their FI [92]. The beneficial effect of dapagliflozin on clinical outcome was observed consistently across the FI values, greater improvement in quality of life with treatment occurred in patients with a higher level of frailty, and there were no differences in the proportions of patients who experienced adverse events or discontinued treatment between dapagliflozin and the placebo [58]. Although this study concluded that SGLT-2is may demonstrate efficacy and safety for HF patients even with frailty, there are several limitations in this study. The FI is derived from a cumulative deficit model composed of symptoms, comorbidities, disabilities, tests of muscle weakness, and laboratory data including indices of malnutrition, kidney failure, anemia, and thyroid hormone. In other words, the FI is a comprehensive vulnerability scale and might not be suitable for the evaluation of physical frailty or sarcopenia alone. Similarly, we can point out this weakness of the FI as an assessment scale of frailty in a sub-analysis of DAPA-HF trial, in which the treatment effect by dapagliflozin on the reduction in primary endpoint reduction was greater in patients with a higher degree of frailty defined by the FI [58]. In the DELIVER trial, despite the absence of exclusion criteria related to a low BMI, the average BMI was as high as 32.1 in the "most frail" group. As mentioned in the previous section, there are substantial differences in body composition or mass between Caucasian and Asian populations [47]. While many Caucasian HF patients are deemed to have sarcopenic obesity, most Asian patients show a low BMI. In this regard, patients with widely varying body

compositions can be uniformly categorized as "frailty". FI is a cumulative deficit model for frailty and does not necessarily evaluate physical function or phenotype. Thus, it needs careful consideration when we determine the efficacy and safety of SGLT-2is for the population with "frailty". In other study, following the sub-analysis of the EMPEROR-Reduced trial, it can be observed that the efficacy of empagliflozin is consistent regardless of BMI, even at <20 kg/m^2 [93]. However, the clinical evidence of SGLT-2is for HF patients with sarcopenia or physical frailty is limited and needs to be explored in the near future.

Table 3. Previous SGLT-2i studies that focused on sarcopenia/frailty, BMI or the elderly.

Population	Study	Topics of Interest (Assessment Tool)	Main Findings
HFrEF	DAPA-HF sub-analysis [57]	Frailty (Frailty index)	The efficacy of dapagliflozin for HFrEF patients was consistent across the range of frailty, and the absolute reductions were larger in more frail patients.
	DAPA-HF sub-analysis [94]	BMI	The efficacy of dapagliflozin for HFrEF patients was consistent across the spectrum of BMI.
	EMPEROR-Reduced sub-analysis [93]	BMI	The efficacy of dapagliflozin for HFrEF patients was consistent across the spectrum of BMI, and weight loss was associated with higher all-cause mortality regardless of BMI groups.
HFpEF	DELIVER sub-analysis [58]	Frailty (Frailty index)	The benefit of dapagliflozin for HFpEF patients was consistent across the range of frailty and the improvement of QOL with medication was greater in those with a higher level of frailty.
	DELIVER sub-analysis [95]	BMI	The benefit of dapagliflozin for HFpEF patients was consistent across the spectrum of BMI.
DM	Kutz et al. (2023) [96]	Frailty (Frailty index)	Medicare beneficiaries with type 2 DM showed greater cardiovascular effectiveness associated with SGLT-2is and GLP-1 receptor agonists than DPP-4 inhibitors.
	EMPA-ELDERLY [97]	Elderly (≥65)	Empagliflozin for elderly T2DM reduced body weight without compromising muscle mass or strength.

SGLT-2i, sodium–glucose cotransporter 2 inhibitor; BMI, body mass index; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; DAPA-HF, Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; EMPEROR-Reduced, The Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and Reduced Ejection Fraction; DELIVER, Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure; EMPA-ELDERLY, Empagliflozin in Elderly T2DM Patients; DM, diabetes mellitus; GLP-1, glucagon-like peptide 1; DPP-4, dipeptidyl-peptidase 4.

A recent study showed SGLT-2is are more efficacious for a primary prevention compared to DPP-4 inhibitors in type 2 DM patients with frailty assessed by FI [96]. This study population included type 2 DM patients over 65 years and patients enrolled in Medicare who initiated treatment with SGLT-2is or DPP-4 inhibitors. SGLT-2is were associated with improved cardiovascular outcomes and all-cause mortality, with the largest absolute benefits among patients with frailty. We should take care in interpreting these data because the FI was used to carry out the frailty assessment and the large number of obese patients included was the same as previous HF studies. Further, genital infections were observed among patients who received SGLT-2i and caused greater harm among more frail patients. Infections can worsen HF and ketoacidosis and are sometimes fatal. Therefore, patients should still be carefully selected for the initiation of SGLT-2is treatment.

SGLT2is have been shown to significantly reduce body weight and fat mass and this effect may be beneficial to improve glycemic control and HF [98]. On the other hand, skeletal muscle mass has also been reported to be significantly reduced [98], although a recent

report showed that empagliflozin induced a significant reduction in body weight, body fat mass and water volume, but the skeletal muscle mass did not change significantly in type 2 DM patients aged ≥ 65 years [97]. Thus, significant concerns have been raised about SGLT-2is' effect on aggravating frailty or sarcopenia. This poses the following question: which patients can safely receive SGLT-2is? Even in DM patients, there is still no unified tool for the assessment of frailty and the guideline recommendations do not address frail older patients [99]. Therefore, it is necessary to consider the metabolic phenotypes of heterogeneous frail patients with DM in order to evaluate the influence of SGLT-2is on these patients. Compared to type I muscle fibers, type II fiber is associated with an increase in insulin resistance via lipid storage in muscle tissue [100]. Aging is related to an increase in insulin resistance followed by a loss of muscle fiber; however, frailty is associated with accelerated muscle loss compared with age alone with a prominent reduction in type II (rather than type I) fibers, which may result in an overall reduction in insulin resistance. Thus, it is important to assess the metabolism spectrum by considering the loss of muscle fibers and body adipose/muscle tissue ratio and not only the BMI. Classification into two phenotypes has been proposed: the anorexic malnourished (A..22..2223M) frail phenotype with significant muscle loss and the sarcopenic obese (SO) frail phenotype with increased visceral fat [99]. SGLT-2is could be effective for SO phenotype patients, but their use for AM phenotype patients may exacerbate sarcopenia. Luseogliflozin and canagliflozin have shown minimal reductions in skeletal muscle mass in not-severely overweight patients with type 2 DM [101–103]. In opposition, dapagliflozin did not show this effect [104] and another study reported that SGLT-2is improve grip strength [105]. Administration of SGLT-2is for AM phenotype patients may lead to an increase in calorie intake and control of weight loss; however, this effect is dependent on the patient's insulin secretory capacity and it is necessary to identify target patients.

5. Future Direction

As discussed above, the most critical issue is that there are few studies validating the efficacy and safety of SGLT-2is for HF patients with physical frailty (not evaluated by the cumulative deficit model) and/or sarcopenia and there have not yet been unified assessment scales for sarcopenia/frailty for HF. In near future further exploration such as basic research (i.e., experiment using cachexia animal model) is necessary to for further understanding of the pathophysiology of sarcopenia and/or physical frailty and the safety and efficacy of SGLT-2is for patients affected with these conditions. Further, we need to develop assessment tool of sarcopenia and/or physical frailty for HF patients which is useful and readily available in various situations in clinical practice, and reassess the efficacy and safety of SGLT-2is by those indicators in specific populations focused on body size, age, gender, and ethnic differences.

6. Conclusions

The efficacy of SGLT-2is for HF patients has been known widely. Beyond the poor definition of frailty of elderly patients suffering from HF, there seems to be an advantage in taking SGLT-2i. However, its long-term safety has not been sufficiently explored and still remains unclear, especially in those with sarcopenia or physical frailty. According to remarkably accelerated aging and increasing prevalence of frailty or sarcopenia in HF population, it is crucial to construct a unified evaluation scale and conduct large-scale clinical trials focusing on the safety and efficacy of SGLT-2is for HF patients with sarcopenia/physical frailty.

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References

1. Gallo, L.A.; Wright, E.M.; Vallon, V. Probing SGLT2 as a therapeutic target for diabetes: Basic physiology and consequences. *Diabetes Vasc. Dis. Res.* **2015**, *12*, 78–89. https://doi.org/10.1177/1479164114561992.
2. Wojcik, C.; Warden, B.A. Mechanisms and Evidence for Heart Failure Benefits from SGLT2 Inhibitors. *Curr. Cardiol. Rep.* **2019**, *21*, 130. https://doi.org/10.1007/s11886-019-1219-4.
3. Zelniker, T.A.; Braunwald, E. Mechanisms of Cardiorenal Effects of Sodium-Glucose Cotransporter 2 Inhibitors: JACC State-of-the-Art Review. *J. Am. Coll. Cardiol.* **2020**, *75*, 422–434. https://doi.org/10.1016/j.jacc.2019.11.031.
4. Hallow, K.M.; Helmlinger, G.; Greasley, P.J.; McMurray, J.J.V.; Boulton, D.W. Why do SGLT2 inhibitors reduce heart failure hospitalization? A differential volume regulation hypothesis. *Diabetes Obes. Metab.* **2018**, *20*, 479–487. https://doi.org/10.1111/dom.13126.
5. Dekkers, C.C.J.; Petrykiv, S.; Laverman, G.D.; Cherney, D.Z.; Gansevoort, R.T.; Heerspink, H.J.L. Effects of the SGLT-2 inhibitor dapagliflozin on glomerular and tubular injury markers. *Diabetes Obes. Metab.* **2018**, *20*, 1988–1993. https://doi.org/10.1111/dom.13301.
6. Verma, S.; McMurray, J.J.V. SGLT2 inhibitors and mechanisms of cardiovascular benefit: A state-of-the-art review. *Diabetologia* **2018**, *61*, 2108–2117. https://doi.org/10.1007/s00125-018-4670-7.
7. Maruyama, T.; Takashima, H.; Oguma, H.; Nakamura, Y.; Ohno, M.; Utsunomiya, K.; Furukawa, T.; Tei, R.; Abe, M. Canagliflozin Improves Erythropoiesis in Diabetes Patients with Anemia of Chronic Kidney Disease. *Diabetes Technol. Ther.* **2019**, *21*, 713–720. https://doi.org/10.1089/dia.2019.0212.
8. Matthews, V.B.; Elliot, R.H.; Rudnicka, C.; Hricova, J.; Herat, L.; Schlaich, M.P. Role of the sympathetic nervous system in regulation of the sodium glucose cotransporter 2. *J. Hypertens.* **2017**, *35*, 2059–2068. https://doi.org/10.1097/hjh.0000000000001434.
9. Herat, L.Y.; Magno, A.L.; Rudnicka, C.; Hricova, J.; Carnagarin, R.; Ward, N.C.; Arcambal, A.; Kiuchi, M.G.; Head, G.A.; Schlaich, M.P.; et al. SGLT2 Inhibitor-Induced Sympathoinhibition: A Novel Mechanism for Cardiorenal Protection. *JACC. Basic Transl. Sci.* **2020**, *5*, 169–179. https://doi.org/10.1016/j.jacbts.2019.11.007.
10. Santos-Gallego, C.G.; Requena-Ibanez, J.A.; San Antonio, R.; Ishikawa, K.; Watanabe, S.; Picatoste, B.; Flores, E.; Garcia-Ropero, A.; Sanz, J.; Hajjar, R.J.; et al. Empagliflozin Ameliorates Adverse Left Ventricular Remodeling in Nondiabetic Heart Failure by Enhancing Myocardial Energetics. *J. Am. Coll. Cardiol.* **2019**, *73*, 1931–1944. https://doi.org/10.1016/j.jacc.2019.01.056.
11. Verma, S.; Rawat, S.; Ho, K.L.; Wagg, C.S.; Zhang, L.; Teoh, H.; Dyck, J.E.; Uddin, G.M.; Oudit, G.Y.; Mayoux, E.; et al. Empagliflozin Increases Cardiac Energy Production in Diabetes: Novel Translational Insights Into the Heart Failure Benefits of SGLT2 Inhibitors. *JACC Basic Transl. Sci.* **2018**, *3*, 575–587. https://doi.org/10.1016/j.jacbts.2018.07.006.
12. Ye, Y.; Bajaj, M.; Yang, H.C.; Perez-Polo, J.R.; Birnbaum, Y. SGLT-2 Inhibition with Dapagliflozin Reduces the Activation of the Nlrp3/ASC Inflammasome and Attenuates the Development of Diabetic Cardiomyopathy in Mice with Type 2 Diabetes. Further Augmentation of the Effects with Saxagliptin, a DPP4 Inhibitor. *Cardiovasc. Drugs Ther.* **2017**, *31*, 119–132. https://doi.org/10.1007/s10557-017-6725-2.
13. Heerspink, H.J.; Perkins, B.A.; Fitchett, D.H.; Husain, M.; Cherney, D.Z. Sodium Glucose Cotransporter 2 Inhibitors in the Treatment of Diabetes Mellitus: Cardiovascular and Kidney Effects, Potential Mechanisms, and Clinical Applications. *Circulation* **2016**, *134*, 752–772. https://doi.org/10.1161/circulationaha.116.021887.
14. Zinman, B.; Wanner, C.; Lachin, J.M.; Fitchett, D.; Bluhmki, E.; Hantel, S.; Mattheus, M.; Devins, T.; Johansen, O.E.; Woerle, H.J.; et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N. Engl. J. Med.* **2015**, *373*, 2117–2128. https://doi.org/10.1056/NEJMoa1504720.
15. Neal, B.; Perkovic, V.; Mahaffey, K.W.; de Zeeuw, D.; Fulcher, G.; Erondu, N.; Shaw, W.; Law, G.; Desai, M.; Matthews, D.R. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N. Engl. J. Med.* **2017**, *377*, 644–657. https://doi.org/10.1056/NEJMoa1611925.
16. Wiviott, S.D.; Raz, I.; Bonaca, M.P.; Mosenzon, O.; Kato, E.T.; Cahn, A.; Silverman, M.G.; Zelniker, T.A.; Kuder, J.F.; Murphy, S.A.; et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *N. Engl. J. Med.* **2019**, *380*, 347–357. https://doi.org/10.1056/NEJMoa1812389.
17. McMurray, J.J.V.; Solomon, S.D.; Inzucchi, S.E.; Køber, L.; Kosiborod, M.N.; Martinez, F.A.; Ponikowski, P.; Sabatine, M.S.; Anand, I.S.; Bělohlávek, J.; et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N. Engl. J. Med.* **2019**, *381*, 1995–2008. https://doi.org/10.1056/NEJMoa1911303.

18. Packer, M.; Anker, S.D.; Butler, J.; Filippatos, G.; Pocock, S.J.; Carson, P.; Januzzi, J.; Verma, S.; Tsutsui, H.; Brueckmann, M.; et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *N. Engl. J. Med.* **2020**, *383*, 1413–1424. https://doi.org/10.1056/NEJMoa2022190.
19. Bhatt, D.L.; Szarek, M.; Steg, P.G.; Cannon, C.P.; Leiter, L.A.; McGuire, D.K.; Lewis, J.B.; Riddle, M.C.; Voors, A.A.; Metra, M.; et al. Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. *N. Engl. J. Med.* **2021**, *384*, 117–128. https://doi.org/10.1056/NEJMoa2030183.
20. Solomon, S.D.; McMurray, J.J.V.; Claggett, B.; de Boer, R.A.; DeMets, D.; Hernandez, A.F.; Inzucchi, S.E.; Kosiborod, M.N.; Lam, C.S.P.; Martinez, F.; et al. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. *N. Engl. J. Med.* **2022**, *387*, 1089–1098. https://doi.org/10.1056/NEJMoa2206286.
21. Anker, S.D.; Butler, J.; Filippatos, G.; Ferreira, J.P.; Bocchi, E.; Böhm, M.; Brunner-La Rocca, H.P.; Choi, D.J.; Chopra, V.; Chuquiure-Valenzuela, E.; et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. *N. Engl. J. Med.* **2021**, *385*, 1451–1461. https://doi.org/10.1056/NEJMoa2107038.
22. Jhund, P.S.; Kondo, T.; Butt, J.H.; Docherty, K.F.; Claggett, B.L.; Desai, A.S.; Vaduganathan, M.; Gasparyan, S.B.; Bengtsson, O.; Lindholm, D.; et al. Dapagliflozin across the range of ejection fraction in patients with heart failure: A patient-level, pooled meta-analysis of DAPA-HF and DELIVER. *Nat. Med.* **2022**, *28*, 1956–1964. https://doi.org/10.1038/s41591-022-01971-4.
23. Heidenreich, P.A.; Bozkurt, B.; Aguilar, D.; Allen, L.A.; Byun, J.J.; Colvin, M.M.; Deswal, A.; Drazner, M.H.; Dunlay, S.M.; Evers, L.R.; 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. https://doi.org/10.1016/j.jacc.2021.12.011.
24. McDonagh, T.A.; Metra, M.; Adamo, M.; Gardner, R.S.; Baumbach, A.; Böhm, M.; Burri, H.; Butler, J.; Čelutkienė, J.; Chioncel, O.; et al. 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur. Heart J.* **2023**, *44*, 3627–3639. https://doi.org/10.1093/eurheartj/ehad195.
25. Evans, M.; Morgan, A.R.; Davies, S.; Beba, H.; Strain, W.D. The role of sodium-glucose co-transporter-2 inhibitors in frail older adults with or without type 2 diabetes mellitus. *Age Ageing* **2022**, *51*, afac201. https://doi.org/10.1093/ageing/afac201.
26. Voors, A.A.; Angermann, C.E.; Teerlink, J.R.; Collins, S.P.; Kosiborod, M.; Biegus, J.; Ferreira, J.P.; Nassif, M.E.; Psotka, M.A.; Tromp, J.; et al. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: A multinational randomized trial. *Nat. Med.* **2022**, *28*, 568–574. https://doi.org/10.1038/s41591-021-01659-1.
27. Lupón, J.; González, B.; Santaeugenia, S.; Altimir, S.; Urrutia, A.; Más, D.; Díez, C.; Pascual, T.; Cano, L.; Valle, V. Prognostic implication of frailty and depressive symptoms in an outpatient population with heart failure. *Rev. Esp. De Cardiol.* **2008**, *61*, 835–842.
28. Forman, D.E.; Fleg, J.L.; Kitzman, D.W.; Brawner, C.A.; Swank, A.M.; McKelvie, R.S.; Clare, R.M.; Ellis, S.J.; Dunlap, M.E.; Bittner, V. 6-min walk test provides prognostic utility comparable to cardiopulmonary exercise testing in ambulatory outpatients with systolic heart failure. *J. Am. Coll. Cardiol.* **2012**, *60*, 2653–2661. https://doi.org/10.1016/j.jacc.2012.08.1010.
29. Tjam, E.Y.; Heckman, G.A.; Smith, S.; Arai, B.; Hirdes, J.; Poss, J.; McKelvie, R.S. Predicting heart failure mortality in frail seniors: Comparing the NYHA functional classification with the Resident Assessment Instrument (RAI) 2.0. *Int. J. Cardiol.* **2012**, *155*, 75–80. https://doi.org/10.1016/j.ijcard.2011.01.031.
30. Khan, H.; Kalogeropoulos, A.P.; Georgiopoulou, V.V.; Newman, A.B.; Harris, T.B.; Rodondi, N.; Bauer, D.C.; Kritchevsky, S.B.; Butler, J. Frailty and risk for heart failure in older adults: The health, aging, and body composition study. *Am. Heart J.* **2013**, *166*, 887–894. https://doi.org/10.1016/j.ahj.2013.07.032.
31. Gastelurrutia, P.; Lupón, J.; Altimir, S.; de Antonio, M.; González, B.; Cabanes, R.; Rodríguez, M.; Urrutia, A.; Domingo, M.; Zamora, E.; et al. Fragility is a key determinant of survival in heart failure patients. *Int. J. Cardiol.* **2014**, *175*, 62–66. https://doi.org/10.1016/j.ijcard.2014.04.237.
32. Lo, A.X.; Donnelly, J.P.; McGwin, G., Jr.; Bittner, V.; Ahmed, A.; Brown, C.J. Impact of gait speed and instrumental activities of daily living on all-cause mortality in adults ≥65 years with heart failure. *Am. J. Cardiol.* **2015**, *115*, 797–801. https://doi.org/10.1016/j.amjcard.2014.12.044.
33. Fülster, S.; Tacke, M.; Sandek, A.; Ebner, N.; Tschöpe, C.; Doehner, W.; Anker, S.D.; von Haehling, S. Muscle wasting in patients with chronic heart failure: Results from the studies investigating co-morbidities aggravating heart failure (SICA-HF). *Eur. Heart J.* **2013**, *34*, 512–519. https://doi.org/10.1093/eurheartj/ehs381.
34. Narumi, T.; Watanabe, T.; Kadowaki, S.; Takahashi, T.; Yokoyama, M.; Kinoshita, D.; Honda, Y.; Funayama, A.; Nishiyama, S.; Takahashi, H.; et al. Sarcopenia evaluated by fat-free mass index is an important prognostic factor in patients with chronic heart failure. *Eur. J. Intern. Med.* **2015**, *26*, 118–122. https://doi.org/10.1016/j.ejim.2015.01.008.
35. Onoue, Y.; Izumiya, Y.; Hanatani, S.; Tanaka, T.; Yamamura, S.; Kimura, Y.; Araki, S.; Sakamoto, K.; Tsujita, K.; Yamamoto, E.; et al. A simple sarcopenia screening test predicts future adverse events in patients with heart failure. *Int. J. Cardiol.* **2016**, *215*, 301–306. https://doi.org/10.1016/j.ijcard.2016.04.128.
36. Funamizu, T.; Nagatomo, Y.; Saji, M.; Iguchi, N.; Daida, H.; Yoshikawa, T. Low muscle mass assessed by psoas muscle area is associated with clinical adverse events in elderly patients with heart failure. *PLoS ONE* **2021**, *16*, e0247140. https://doi.org/10.1371/journal.pone.0247140.
37. Konishi, M.; Kagiyama, N.; Kamiya, K.; Saito, H.; Saito, K.; Ogasahara, Y.; Maekawa, E.; Misumi, T.; Kitai, T.; Iwata, K.; et al. Impact of sarcopenia on prognosis in patients with heart failure with reduced and preserved ejection fraction. *Eur. J. Prev. Cardiol.* **2021**, *28*, 1022–1029. https://doi.org/10.1093/eurjpc/zwaa117.

38. Shimokawa, H.; Miura, M.; Nochioka, K.; Sakata, Y. Heart failure as a general pandemic in Asia. *Eur. J. Heart Fail.* **2015**, *17*, 884–892. https://doi.org/10.1002/ejhf.319.
39. Cieza, A.; Causey, K.; Kamenov, K.; Hanson, S.W.; Chatterji, S.; Vos, T. Global estimates of the need for rehabilitation based on the Global Burden of Disease study 2019: A systematic analysis for the Global Burden of Disease Study 2019. *Lancet* **2021**, *396*, 2006–2017. https://doi.org/10.1016/s0140-6736(20)32340-0.
40. Guralnik, J.M.; Ferrucci, L.; Pieper, C.F.; Leveille, S.G.; Markides, K.S.; Ostir, G.V.; Studenski, S.; Berkman, L.F.; Wallace, R.B. Lower extremity function and subsequent disability: Consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery. *J. Gerontol. Ser. A Biol. Sci. Med. Sci.* **2000**, *55*, M221-231. https://doi.org/10.1093/gerona/55.4.m221.
41. Podsiadlo, D.; Richardson, S. The timed "Up & Go": A test of basic functional mobility for frail elderly persons. *J. Am. Geriatr. Soc.* **1991**, *39*, 142–148. https://doi.org/10.1111/j.1532-5415.1991.tb01616.x.
42. Rockwood, K.; Mitnitski, A. Frailty in relation to the accumulation of deficits. *J. Gerontol. Ser. A Biol. Sci. Med. Sci.* **2007**, *62*, 722–727. https://doi.org/10.1093/gerona/62.7.722.
43. Mahoney, F.I.; Barthel, D.W. Functional Evaluation: The Barthel Index. *Md. State Med. J.* **1965**, *14*, 61–65.
44. Rockwood, K.; Song, X.; MacKnight, C.; Bergman, H.; Hogan, D.B.; McDowell, I.; Mitnitski, A. A global clinical measure of fitness and frailty in elderly people. *CMAJ Can. Med. Assoc. J. = J. De L'association Med. Can.* **2005**, *173*, 489–495. https://doi.org/10.1503/cmaj.050051.
45. Fried, L.P.; Tangen, C.M.; Walston, J.; Newman, A.B.; Hirsch, C.; Gottdiener, J.; Seeman, T.; Tracy, R.; Kop, W.J.; Burke, G.; et al. Frailty in older adults: Evidence for a phenotype. *J. Gerontol. Ser. A Biol. Sci. Med. Sci.* **2001**, *56*, M146–M156. https://doi.org/10.1093/gerona/56.3.m146.
46. American Diabetes Association Professional Practice Committee. 13. Older Adults: Standards of Care in Diabetes-2024. *Diabetes Care* **2024**, *47*, S244-S257. https://doi.org/10.2337/dc24-S013.
47. Finucane, M.M.; Stevens, G.A.; Cowan, M.J.; Danaei, G.; Lin, J.K.; Paciorek, C.J.; Singh, G.M.; Gutierrez, H.R.; Lu, Y.; Bahalim, A.N.; et al. National, regional, and global trends in body-mass index since 1980: Systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9·1 million participants. *Lancet* **2011**, *377*, 557–567. https://doi.org/10.1016/s0140-6736(10)62037-5.
48. Goodpaster, B.H.; Park, S.W.; Harris, T.B.; Kritchevsky, S.B.; Nevitt, M.; Schwartz, A.V.; Simonsick, E.M.; Tylavsky, F.A.; Visser, M.; Newman, A.B. The loss of skeletal muscle strength, mass, and quality in older adults: The health, aging and body composition study. *J. Gerontol. Ser. A Biol. Sci. Med. Sci.* **2006**, *61*, 1059–1064. https://doi.org/10.1093/gerona/61.10.1059.
49. Delmonico, M.J.; Harris, T.B.; Lee, J.S.; Visser, M.; Nevitt, M.; Kritchevsky, S.B.; Tylavsky, F.A.; Newman, A.B. Alternative definitions of sarcopenia, lower extremity performance, and functional impairment with aging in older men and women. *J. Am. Geriatr. Soc.* **2007**, *55*, 769–774. https://doi.org/10.1111/j.1532-5415.2007.01140.x.
50. Cruz-Jentoft, A.J.; Baeyens, J.P.; Bauer, J.M.; Boirie, Y.; Cederholm, T.; Landi, F.; Martin, F.C.; Michel, J.P.; Rolland, Y.; Schneider, S.M.; et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. *Age Ageing* **2010**, *39*, 412–423. https://doi.org/10.1093/ageing/afq034.
51. Cruz-Jentoft, A.J.; Bahat, G.; Bauer, J.; Boirie, Y.; Bruyère, O.; Cederholm, T.; Cooper, C.; Landi, F.; Rolland, Y.; Sayer, A.A.; et al. Sarcopenia: Revised European consensus on definition and diagnosis. *Age Ageing* **2019**, *48*, 16–31. https://doi.org/10.1093/ageing/afy169.
52. Chen, L.K.; Woo, J.; Assantachai, P.; Auyeung, T.W.; Chou, M.Y.; Iijima, K.; Jang, H.C.; Kang, L.; Kim, M.; Kim, S.; et al. Asian Working Group for Sarcopenia: 2019 Consensus Update on Sarcopenia Diagnosis and Treatment. *J. Am. Med. Dir. Assoc.* **2020**, *21*, 300–307.e302. https://doi.org/10.1016/j.jamda.2019.12.012.
53. Richter, D.; Guasti, L.; Walker, D.; Lambrinou, E.; Lionis, C.; Abreu, A.; Savelieva, I.; Fumagalli, S.; Bo, M.; Rocca, B.; et al. Frailty in cardiology: Definition, assessment and clinical implications for general cardiology. A consensus document of the Council for Cardiology Practice (CCP), Association for Acute Cardio Vascular Care (ACVC), Association of Cardiovascular Nursing and Allied Professions (ACNAP), European Association of Preventive Cardiology (EAPC), European Heart Rhythm Association (EHRA), Council on Valvular Heart Diseases (VHD), Council on Hypertension (CHT), Council of Cardio-Oncology (CCO), Working Group (WG) Aorta and Peripheral Vascular Diseases, WG e-Cardiology, WG Thrombosis, of the European Society of Cardiology, European Primary Care Cardiology Society (EPCCS). *Eur. J. Prev. Cardiol.* **2022**, *29*, 216–227. https://doi.org/10.1093/eurjpc/zwaa167.
54. Gorodeski, E.Z.; Goyal, P.; Hummel, S.L.; Krishnaswami, A.; Goodlin, S.J.; Hart, L.L.; Forman, D.E.; Wenger, N.K.; Kirkpatrick, J.N.; Alexander, K.P. Domain Management Approach to Heart Failure in the Geriatric Patient: Present and Future. *J. Am. Coll. Cardiol.* **2018**, *71*, 1921–1936. https://doi.org/10.1016/j.jacc.2018.02.059.
55. Dent, E.; Kowal, P.; Hoogendijk, E.O. Frailty measurement in research and clinical practice: A review. *Eur. J. Intern. Med.* **2016**, *31*, 3–10. https://doi.org/10.1016/j.ejim.2016.03.007.
56. Chokshi, N.B.K.; Karmakar, B.; Pathan, S.K.; Joshi, V.; Gohel, D.M.; Coulshed, D.S.; Negishi, K.; Pathan, F.K. A Systematic Review of Frailty Scores Used in Heart Failure Patients. *Heart Lung Circ.* **2023**, *32*, 441–453. https://doi.org/10.1016/j.hlc.2023.01.011.
57. Butt, J.H.; Dewan, P.; Merkely, B.; Belohlávek, J.; Drożdż, J.; Kitakaze, M.; Inzucchi, S.E.; Kosiborod, M.N.; Martinez, F.A.; Tereshchenko, S.; et al. Efficacy and Safety of Dapagliflozin According to Frailty in Heart Failure With Reduced Ejection Fraction : A Post Hoc Analysis of the DAPA-HF Trial. *Ann. Intern. Med.* **2022**, *175*, 820–830. https://doi.org/10.7326/m21-4776.

58. Butt, J.H.; Jhund, P.S.; Belohlávek, J.; de Boer, R.A.; Chiang, C.E.; Desai, A.S.; Drożdż, J.; Hernandez, A.F.; Inzucchi, S.E.; Katova, T.; et al. Efficacy and Safety of Dapagliflozin According to Frailty in Patients With Heart Failure: A Prespecified Analysis of the DELIVER Trial. *Circulation* **2022**, *146*, 1210–1224. https://doi.org/10.1161/circulationaha.122.061754.
59. To, T.L.; Doan, T.N.; Ho, W.C.; Liao, W.C. Prevalence of Frailty among Community-Dwelling Older Adults in Asian Countries: A Systematic Review and Meta-Analysis. *Healthcare* **2022**, *10*, 895. https://doi.org/10.3390/healthcare10050895.
60. Da Mata, F.A.; Pereira, P.P.; Andrade, K.R.; Figueiredo, A.C.; Silva, M.T.; Pereira, M.G. Prevalence of Frailty in Latin America and the Caribbean: A Systematic Review and Meta-Analysis. *PLoS ONE* **2016**, *11*, e0160019. https://doi.org/10.1371/journal.pone.0160019.
61. Collard, R.M.; Boter, H.; Schoevers, R.A.; Oude Voshaar, R.C. Prevalence of frailty in community-dwelling older persons: A systematic review. *J. Am. Geriatr. Soc.* **2012**, *60*, 1487–1492. https://doi.org/10.1111/j.1532-5415.2012.04054.x.
62. O'Caoimh, R.; Galluzzo, L.; Rodríguez-Laso, Á.; Van der Heyden, J.; Ranhoff, A.H.; Lamprini-Koula, M.; Ciutan, M.; López-Samaniego, L.; Carcaillon-Bentata, L.; Kennelly, S.; et al. Prevalence of frailty at population level in European ADVANTAGE Joint Action Member States: A systematic review and meta-analysis. *Ann. Dell'istituto Super. Di Sanita* **2018**, *54*, 226–238. https://doi.org/10.4415/ann_18_03_10.
63. O'Caoimh, R.; Sezgin, D.; O'Donovan, M.R.; Molloy, D.W.; Clegg, A.; Rockwood, K.; Liew, A. Prevalence of frailty in 62 countries across the world: A systematic review and meta-analysis of population-level studies. *Age Ageing* **2021**, *50*, 96–104. https://doi.org/10.1093/ageing/afaa219.
64. von Haehling, S.; Lainscak, M.; Springer, J.; Anker, S.D. Cardiac cachexia: A systematic overview. *Pharmacol. Ther.* **2009**, *121*, 227–252. https://doi.org/10.1016/j.pharmthera.2008.09.009.
65. Kazemi-Bajestani, S.M.; Becher, H.; Fassbender, K.; Chu, Q.; Baracos, V.E. Concurrent evolution of cancer cachexia and heart failure: Bilateral effects exist. *J. Cachexia Sarcopenia Muscle* **2014**, *5*, 95–104. https://doi.org/10.1007/s13539-014-0137-y.
66. Xue, Q.L.; Bandeen-Roche, K.; Varadhan, R.; Zhou, J.; Fried, L.P. Initial manifestations of frailty criteria and the development of frailty phenotype in the Women's Health and Aging Study II. *J. Gerontol. Ser. A Biol. Sci. Med. Sci.* **2008**, *63*, 984–990. https://doi.org/10.1093/gerona/63.9.984.
67. Talha, K.M.; Pandey, A.; Fudim, M.; Butler, J.; Anker, S.D.; Khan, M.S. Frailty and heart failure: State-of-the-art review. *J. Cachexia Sarcopenia Muscle* **2023**, *14*, 1959–1972. https://doi.org/10.1002/jcsm.13306.
68. Ijaz, N.; Buta, B.; Xue, Q.L.; Mohess, D.T.; Bushan, A.; Tran, H.; Batchelor, W.; deFilippi, C.R.; Walston, J.D.; Bandeen-Roche, K.; et al. Interventions for Frailty Among Older Adults With Cardiovascular Disease: JACC State-of-the-Art Review. *J. Am. Coll. Cardiol.* **2022**, *79*, 482–503. https://doi.org/10.1016/j.jacc.2021.11.029.
69. Vitale, C.; Uchmanowicz, I. Frailty in patients with heart failure. *Eur. Heart J. Suppl. J. Eur. Soc. Cardiol.* **2019**, *21*, L12–L16. https://doi.org/10.1093/eurheartj/suz238.
70. Vitale, C.; Spoletini, I.; Rosano, G.M. Frailty in Heart Failure: Implications for Management. *Card. Fail. Rev.* **2018**, *4*, 104–106. https://doi.org/10.15420/cfr.2018.22.2.
71. Pandey, A.; Kitzman, D.; Reeves, G. Frailty Is Intertwined With Heart Failure: Mechanisms, Prevalence, Prognosis, Assessment, and Management. *JACC. Heart Fail.* **2019**, *7*, 1001–1011. https://doi.org/10.1016/j.jchf.2019.10.005.
72. Dewan, P.; Jackson, A.; Jhund, P.S.; Shen, L.; Ferreira, J.P.; Petrie, M.C.; Abraham, W.T.; Desai, A.S.; Dickstein, K.; Køber, L.; et al. The prevalence and importance of frailty in heart failure with reduced ejection fraction—An analysis of PARADIGM-HF and ATMOSPHERE. *Eur. J. Heart Fail.* **2020**, *22*, 2123–2133. https://doi.org/10.1002/ejhf.1832.
73. Pandey, A.; Segar, M.W.; Singh, S.; Reeves, G.R.; O'Connor, C.; Piña, I.; Whellan, D.; Kraus, W.E.; Mentz, R.J.; Kitzman, D.W. Frailty Status Modifies the Efficacy of Exercise Training Among Patients With Chronic Heart Failure and Reduced Ejection Fraction: An Analysis From the HF-ACTION Trial. *Circulation* **2022**, *146*, 80–90. https://doi.org/10.1161/circulationaha.122.059983.
74. Vidán, M.T.; Blaya-Novakova, V.; Sánchez, E.; Ortiz, J.; Serra-Rexach, J.A.; Bueno, H. Prevalence and prognostic impact of frailty and its components in non-dependent elderly patients with heart failure. *Eur. J. Heart Fail.* **2016**, *18*, 869–875. https://doi.org/10.1002/ejhf.518.
75. Yang, X.; Lupón, J.; Vidán, M.T.; Ferguson, C.; Gastelurrutia, P.; Newton, P.J.; Macdonald, P.S.; Bueno, H.; Bayés-Genís, A.; Woo, J.; et al. Impact of Frailty on Mortality and Hospitalization in Chronic Heart Failure: A Systematic Review and Meta-Analysis. *J. Am. Heart Assoc.* **2018**, *7*, e008251. https://doi.org/10.1161/jaha.117.008251.
76. Duggan, E.; Knight, S.P.; Xue, F.; Romero-Ortuno, R. Haemodynamic Parameters Underlying the Relationship between Sarcopenia and Blood Pressure Recovery on Standing. *J. Clin. Med.* **2023**, *13*, 18. https://doi.org/10.3390/jcm13010018.
77. Axelrod, C.L.; Dantas, W.S.; Kirwan, J.P. Sarcopenic obesity: Emerging mechanisms and therapeutic potential. *Metab. Clin. Exp.* **2023**, *146*, 155639. https://doi.org/10.1016/j.metabol.2023.155639.
78. Ding, J.; Kritchevsky, S.B.; Newman, A.B.; Taaffe, D.R.; Nicklas, B.J.; Visser, M.; Lee, J.S.; Nevitt, M.; Tylavsky, F.A.; Rubin, S.M.; et al. Effects of birth cohort and age on body composition in a sample of community-based elderly. *Am. J. Clin. Nutr.* **2007**, *85*, 405–410. https://doi.org/10.1093/ajcn/85.2.405.
79. Frontera, W.R.; Hughes, V.A.; Fielding, R.A.; Fiatarone, M.A.; Evans, W.J.; Roubenoff, R. Aging of skeletal muscle: A 12-yr longitudinal study. *J. Appl. Physiol.* **2000**, *88*, 1321–1326. https://doi.org/10.1152/jappl.2000.88.4.1321.
80. Upadhya, B.; Haykowsky, M.J.; Eggebeen, J.; Kitzman, D.W. Sarcopenic obesity and the pathogenesis of exercise intolerance in heart failure with preserved ejection fraction. *Curr. Heart Fail. Rep.* **2015**, *12*, 205–214. https://doi.org/10.1007/s11897-015-0257-5.

81. Fontana, L.; Eagon, J.C.; Trujillo, M.E.; Scherer, P.E.; Klein, S. Visceral fat adipokine secretion is associated with systemic inflammation in obese humans. *Diabetes* **2007**, *56*, 1010–1013. https://doi.org/10.2337/db06-1656.
82. Goodpaster, B.H.; Brown, N.F. Skeletal muscle lipid and its association with insulin resistance: What is the role for exercise? *Exerc. Sport Sci. Rev.* **2005**, *33*, 150–154. https://doi.org/10.1097/00003677-200507000-00008.
83. Batsis, J.A.; Mackenzie, T.A.; Lopez-Jimenez, F.; Bartels, S.J. Sarcopenia, sarcopenic obesity, and functional impairments in older adults: National Health and Nutrition Examination Surveys 1999–2004. *Nutr. Res.* **2015**, *35*, 1031–1039. https://doi.org/10.1016/j.nutres.2015.09.003.
84. Fonseca, G.; Dos Santos, M.R.; de Souza, F.R.; Takayama, L.; Rodrigues Pereira, R.M.; Negrão, C.E.; Alves, M.N.N. Discriminating sarcopenia in overweight/obese male patients with heart failure: The influence of body mass index. *ESC Heart Fail.* **2020**, *7*, 84–91. https://doi.org/10.1002/ehf2.12545.
85. Roh, E.; Choi, K.M. Health Consequences of Sarcopenic Obesity: A Narrative Review. *Front. Endocrinol.* **2020**, *11*, 332. https://doi.org/10.3389/fendo.2020.00332.
86. Saito, H.; Matsue, Y.; Kamiya, K.; Kagiyama, N.; Maeda, D.; Endo, Y.; Ueno, H.; Yoshioka, K.; Mizukami, A.; Saito, K.; et al. Sarcopenic obesity is associated with impaired physical function and mortality in older patients with heart failure: Insight from FRAGILE-HF. *BMC Geriatr.* **2022**, *22*, 556. https://doi.org/10.1186/s12877-022-03168-3.
87. Billingsley, H.E.; Del Buono, M.G.; Canada, J.M.; Kim, Y.; Damonte, J.I.; Trankle, C.R.; Halasz, G.; Mihalick, V.; Vecchié, A.; Markley, R.R.; et al. Sarcopenic Obesity Is Associated With Reduced Cardiorespiratory Fitness Compared With Nonsarcopenic Obesity in Patients With Heart Failure With Reduced Ejection Fraction. *Circulation. Heart Fail.* **2022**, *15*, e009518. https://doi.org/10.1161/circheartfailure.122.009518.
88. Kato, E.T.; Silverman, M.G.; Mosenzon, O.; Zelniker, T.A.; Cahn, A.; Furtado, R.H.M.; Kuder, J.; Murphy, S.A.; Bhatt, D.L.; Leiter, L.A.; et al. Effect of Dapagliflozin on Heart Failure and Mortality in Type 2 Diabetes Mellitus. *Circulation* **2019**, *139*, 2528–2536. https://doi.org/10.1161/circulationaha.119.040130.
89. Rådholm, K.; Figtree, G.; Perkovic, V.; Solomon, S.D.; Mahaffey, K.W.; de Zeeuw, D.; Fulcher, G.; Barrett, T.D.; Shaw, W.; Desai, M.; et al. Canagliflozin and Heart Failure in Type 2 Diabetes Mellitus: Results From the CANVAS Program. *Circulation* **2018**, *138*, 458–468. https://doi.org/10.1161/circulationaha.118.034222.
90. Packer, M.; Anker, S.D.; Butler, J.; Filippatos, G.; Ferreira, J.P.; Pocock, S.J.; Carson, P.; Anand, I.; Doehner, W.; Haass, M.; et al. Effect of Empagliflozin on the Clinical Stability of Patients With Heart Failure and a Reduced Ejection Fraction: The EMPEROR-Reduced Trial. *Circulation* **2021**, *143*, 326–336. https://doi.org/10.1161/circulationaha.120.051783.
91. Docherty, K.F.; Jhund, P.S.; Anand, I.; Bengtsson, O.; Böhm, M.; de Boer, R.A.; DeMets, D.L.; Desai, A.S.; Drozdz, J.; Howlett, J.; et al. Effect of Dapagliflozin on Outpatient Worsening of Patients With Heart Failure and Reduced Ejection Fraction: A Prespecified Analysis of DAPA-HF. *Circulation* **2020**, *142*, 1623–1632. https://doi.org/10.1161/circulationaha.120.047480.
92. Mitnitski, A.B.; Mogilner, A.J.; Rockwood, K. Accumulation of deficits as a proxy measure of aging. *Sci. World J.* **2001**, *1*, 323–336. https://doi.org/10.1100/tsw.2001.58.
93. Anker, S.D.; Khan, M.S.; Butler, J.; Ofstad, A.P.; Peil, B.; Pfarr, E.; Doehner, W.; Sattar, N.; Coats, A.J.S.; Filippatos, G.; et al. Weight change and clinical outcomes in heart failure with reduced ejection fraction: Insights from EMPEROR-Reduced. *Eur. J. Heart Fail.* **2023**, *25*, 117–127. https://doi.org/10.1002/ejhf.2728.
94. Adamson, C.; Jhund, P.S.; Docherty, K.F.; Bělohlávek, J.; Chiang, C.E.; Diez, M.; Drożdż, J.; Dukát, A.; Howlett, J.; Ljungman, C.E.A.; et al. Efficacy of dapagliflozin in heart failure with reduced ejection fraction according to body mass index. *Eur. J. Heart Fail.* **2021**, *23*, 1662–1672. https://doi.org/10.1002/ejhf.2308.
95. Adamson, C.; Kondo, T.; Jhund, P.S.; de Boer, R.A.; Cabrera Honorio, J.W.; Claggett, B.; Desai, A.S.; Alcocer Gamba, M.A.; Al Habeeb, W.; Hernandez, A.F.; et al. Dapagliflozin for heart failure according to body mass index: The DELIVER trial. *Eur. Heart J.* **2022**, *43*, 4406–4417. https://doi.org/10.1093/eurheartj/ehac481.
96. Kutz, A.; Kim, D.H.; Wexler, D.J.; Liu, J.; Schneeweiss, S.; Glynn, R.J.; Patorno, E. Comparative Cardiovascular Effectiveness and Safety of SGLT-2 Inhibitors, GLP-1 Receptor Agonists, and DPP-4 Inhibitors According to Frailty in Type 2 Diabetes. *Diabetes Care* **2023**, *46*, 2004–2014. https://doi.org/10.2337/dc23-0671.
97. Yabe, D.; Shiki, K.; Homma, G.; Meinicke, T.; Ogura, Y.; Seino, Y. Efficacy and safety of the sodium-glucose co-transporter-2 inhibitor empagliflozin in elderly Japanese adults (≥65 years) with type 2 diabetes: A randomized, double-blind, placebo-controlled, 52-week clinical trial (EMPA-ELDERLY). *Diabetes Obes. Metab.* **2023**, *25*, 3538–3548. https://doi.org/10.1111/dom.15249.
98. Zhang, S.; Qi, Z.; Wang, Y.; Song, D.; Zhu, D. Effect of sodium-glucose transporter 2 inhibitors on sarcopenia in patients with type 2 diabetes mellitus: A systematic review and meta-analysis. *Front. Endocrinol.* **2023**, *14*, 1203666. https://doi.org/10.3389/fendo.2023.1203666.
99. Sinclair, A.J.; Pennells, D.; Abdelhafiz, A.H. Hypoglycaemic therapy in frail older people with type 2 diabetes mellitus-a choice determined by metabolic phenotype. *Aging Clin. Exp. Res.* **2022**, *34*, 1949–1967. https://doi.org/10.1007/s40520-022-02142-8.
100. Pette, D.; Peuker, H.; Staron, R.S. The impact of biochemical methods for single muscle fibre analysis. *Acta Physiol. Scand.* **1999**, *166*, 261–277. https://doi.org/10.1046/j.1365-201x.1999.00568.x.
101. Sasaki, T.; Sugawara, M.; Fukuda, M. Sodium-glucose cotransporter 2 inhibitor-induced changes in body composition and simultaneous changes in metabolic profile: 52-week prospective LIGHT (Luseogliflozin: The Components of Weight Loss in Japanese Patients with Type 2 Diabetes Mellitus) Study. *J. Diabetes Investig.* **2019**, *10*, 108–117. https://doi.org/10.1111/jdi.12851.

102. Bouchi, R.; Terashima, M.; Sasahara, Y.; Asakawa, M.; Fukuda, T.; Takeuchi, T.; Nakano, Y.; Murakami, M.; Minami, I.; Izumiyama, H.; et al. Luseogliflozin reduces epicardial fat accumulation in patients with type 2 diabetes: A pilot study. *Cardiovasc. Diabetol.* **2017**, *16*, 32. https://doi.org/10.1186/s12933-017-0516-8.
103. Cefalu, W.T.; Leiter, L.A.; Yoon, K.H.; Arias, P.; Niskanen, L.; Xie, J.; Balis, D.A.; Canovatchel, W.; Meininger, G. Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 3 non-inferiority trial. *Lancet* **2013**, *382*, 941–950. https://doi.org/10.1016/s0140-6736(13)60683-2.
104. Sugiyama, S.; Jinnouchi, H.; Kurinami, N.; Hieshima, K.; Yoshida, A.; Jinnouchi, K.; Nishimura, H.; Suzuki, T.; Miyamoto, F.; Kajiwara, K.; et al. Dapagliflozin Reduces Fat Mass without Affecting Muscle Mass in Type 2 Diabetes. *J. Atheroscler. Thromb.* **2018**, *25*, 467–476. https://doi.org/10.5551/jat.40873.
105. Sano, M.; Meguro, S.; Kawai, T.; Suzuki, Y. Increased grip strength with sodium-glucose cotransporter 2. *J. Diabetes* **2016**, *8*, 736–737. https://doi.org/10.1111/1753-0407.12402.