Sodium-glucose cotransporter 2 inhibitors and heart failure decompensation: considerations on body composition and skeletal mass

To the editor We read with great interest the results of the study by Wawrzeńczyk et al,[1] who showed that individuals hospitalized due to decompensation of chronic heart failure (CHF) face a greater nutritional risk, with a significant decrease in skeletal muscle mass (SMM) by 2.5 kg and in skeletal muscle index, by 0.8 kg/m^2, compared with controls. Notably, patients with an SMM of 45.5% or greater (expressed as percentage of fat-free mass) experienced a significant 9-fold increase in the odds of death.[1]

Sodium-glucose cotransporter 2 (SGLT-2) inhibitors, primarily developed as a drug class for patients with type 2 diabetes mellitus (T2DM), have now been established as a treatment option in individuals with CHF, according to the most recent guidelines. They have been shown to significantly decrease the risk for hospitalization due to decompensation of CHF.[2] In the acute setting, they have been proven to decrease the risk for a combined end point of worsening heart failure (HF), rehospitalization for HF or death at 60 days, despite the fact that they do not improve symptoms, diuretic response, and levels of N-terminal pro–B-type natriuretic peptide or shorten the length of hospital stay.[3] Therefore, there is a vivid and ongoing discussion on whether SGLT-2 inhibitors should be continued or started in individuals with acute HF or decompensation of CHF.

SGLT-2 inhibitors decrease body weight, mainly due to net caloric loss in the context of glucosuria. They have been also shown to decrease total fat mass when administered in patients with T2DM receiving insulin treatment.[4] A numerical but statistically insignificant decrease in SMM was demonstrated.[4] There is an ongoing randomized controlled trial that will assess the effect of long-term treatment with SGLT-2 inhibitors on SMM in elderly patients with T2DM.[5]

Therefore, since more than half of patients included in the study by Wawrzeńczyk et al[1] had a previous diagnosis of T2DM, it would be of great interest to know how many of them were taking SGLT-2 inhibitors prior to enrollment and if there was a difference in SMM between individuals treated with SGLT-2 inhibitors and those that were not. The latter analysis will provide some useful insights into the mechanisms of action of SGLT-2 inhibitors.

ARTICLE INFORMATION

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Authors' reply We thank Patoulias and colleagues for their interest in our manuscript.[1] The authors of the letter raise a very important issue in

the treatment of patients with chronic heart failure (CHF); namely, the risk for sarcopenia and the potential unfavorable effect of sodium-glucose cotransporter 2 (SGLT-2) inhibitors on skeletal muscle mass (SMM). Sarcopenia, which has recently been newly defined as a functional disability involving weakness of muscle strength and a reduction in whole-body SMM,[2] is recognized as a general predictor of all-cause mortality and frailty, and is also linked with a reduced peak oxygen consumption and shorter exercise time, particularly in patients with CHF.[3] The available data show a weight-lowering effect of empagliflozin, dapagliflozin, ipragliflozin, luseogliflozin, and canagliflozin administered for 24 to 52 weeks with or without metformin.[4-5] This effect was associated with a reduction in total, visceral, and epicardial fat, which is recognized as one of the cardioprotective properties of flozins, and with a mainly nonsignificant influence on SMM, but with improvement in the endocrine function of the skeletal muscle (eg, reduction in blood concentration of myostatin) and metabolic functions (eg, decrease in insulin resistance). However, so far, the favorable effect of SGLT-2 inhibitors on body composition was shown only in patients with type 1 and 2 diabetes mellitus (DM), but not in those with CHF. In light of this, the question raised by Patoulias and colleagues is of great clinical importance, especially as SGLT-2 inhibitors have become one of 5 first-line classes of drugs dedicated to treatment of patients with CHF, both with and without DM.[5] In our study, we found an almost 10-fold higher risk of all-cause readmission in patients with a visceral fat level (VFL) score greater than 15, suggesting that VFL acts as the main body composition target of SGLT-2 inhibitors in CHF patients. Such assumption corroborates the outcomes of the DAPA-HF (Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure) and EMPEROR-Reduced (Empagliflozin Outcom Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction) trials.[5] Unfortunately, in our investigation, none of the CHF patients were treated with SGLT-2 inhibitors, which can be explained by the study enrollment period (May 2016–February 2018), high costs of treatment with SGLT-2 inhibitors, their relatively short availability on the Polish market (about 6 years) as well as the fact that they had only recently been included in the standard therapy of CHF.[5]

While preparing this reply, we also reanalyzed our database. We discovered, among other things, that CHF patients with type 2 DM seemed more likely to benefit from therapy with SGLT-2 inhibitors compared with nondiabetic individuals. For example, they had a significantly higher body mass index (BMI), waist circumference, waist-to-hip ratio, waist-to-height ratio, fat mass (FM), and VFL, as well as a lower percentage of SMM in whole body weight (SMM%). On the other hand, there were no significant differences between CHF patients with and without type 2 DM in the Mini Nutritional Assessment score and SMM expressed in kilograms. These differences in nutritional statuses of the patients were associated with a significantly higher Borg Dyspnea Scale score and significantly shorter distance during a 6-minute walk test in patients with DM compared with nondiabetic individuals, but without significant differences in Barthel scale score or handgrip strength. Among the parameters of nutritional status assessment in CHF patients, a higher SMM% was associated with a higher rate of all-cause mortality, higher VFL increased the risk of all-cause readmission, and a lower percentage of FM in whole body mass (FM%) was associated with a shorter length of hospital stay.[1] Of note, absolute SMM and FM expressed in kilograms, which would seem to be better indicators of a potential weight-reducing effect of SGLT-2 inhibitors than the relative biomarkers (SMM% and FM%), did not influence patients' prognoses. As a result of the limitations of the body composition assessment method mentioned in our study (the use of only 2 frequencies in the bioelectrical impedance analysis and calculation of body composition parameters based on algorithms provided by the manufacturer of the device),[1] the relative increase in SMM% and decrease in FM% found in our study can also be interpreted as having resulted from water retention (more severe CHF advancement), which, in turn, might suggest greater importance of the diuretic compared with the weight-decreasing effect of SGLT-2 inhibitors in CHF patients. Therefore, the mechanism of SGLT-2 inhibitors in CHF patients requires further study, especially in the context of the still undetermined clinical importance of the so-called "obesity paradox" or "BMI paradox." Also, the role of adipose tissue distribution, body composition, and the prognostic effect of their potential modification by treatment with SGLT-2 inhibitors in patients with CHF should be further investigated.

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