Research Letter

Empagliflozin Targeting the Real-World Heart Failure Population

To the Editor:

Heart failure (HF) is a complex syndrome further aggravated by diabetes mellitus (DM). In the EMPA-REG OUTCOME trial, enrolling 7020 patients with diabetes, established cardiovascular (CV) disease, Hb_{A1c} 7.0%−10%, and estimated glomerular filtration rate (eGFR) ≥30 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$, empagliflozin significantly reduced hospitalization for HF.[1] However, only 10.1% had HF at baseline. We aimed to investigate whether patients with diabetes admitted for decompensated HF in a "real-world" setting would be enrolled per the trial's main key inclusion and exclusion criteria.

This study was based on the PRO-IRON prospective cohort, enrolling 771 consecutive patients admitted to an internal medicine ward.[2] HF diagnosis was based on electronic medical record review. Patients were defined as candidates for empagliflozin if they met the key inclusion criteria (ie, Hb_{A1c} 7%−10%, high risk for CV events, and eGFR ≥30 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ at discharge). In addition, the European Medical Agency (EMA) and US Food and Drug Administration (FDA) restrictions on empagliflozin were considered.

HF was present in 41.1% (n = 317) of the overall cohort and of these, 40.4% (n = 128) had diabetes. Nine patients were excluded because of in-hospital death, leaving 119 patients. The mean age was 76.8 ± 10.0 years, and 37.8% were male. Most patients had HF with preserved ejection fraction (68.1%). Hypertension (59.7%) and ischemia (33.6%) were the most prevalent etiologies.

In this diabetic HF cohort (n = 119), only 17.6% (n = 21) would have been enrolled in the EMPA-REG OUTCOME trial, in which study participants were significantly younger and had more ischemic heart disease and HF with reduced ejection fraction (HFrEF). Considering the EMA recommendations (eGFR ≥60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$), only 8 patients (6.7%) would have been potential candidates. Similarly, considering the FDA recommendations (eGFR ≥45 patients), only 13 patients (10.9%) would have been selected (Fig. 1). Overall, 57.1% (n = 68) were excluded because of Hb_{A1c} off target, 55.5% (n = 66) because of absence of high CV risk, and 14.3% (n = 17) because of eGFR <30 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$. When analyzing the 98 excluded patients, 31 (31.6%) might have been candidates if their Hb_{A1c} rose or fell to 7.0%−10% and 95 (96.9%) would have been suitable if their CV risk was not taken into account, because HF was not a criterion for high CV risk in the EMPA-REG OUTCOME trial.

Our results were primarily driven by the lack of "high CV risk." Whether patients without a CV major event would benefit from this drug (ie, as primary prevention) is not established. In this regard, it should be noted that the CANVAS trial, investigating canagliflozin, has shown a greater reduction in the composite end point (CV death, nonfatal myocardial infarction, and nonfatal stroke) and HF hospitalization in the high-CV-risk group (as secondary prevention) compared with the low-CV-risk group (as primary prevention).[3]

A demanding eGFR cutoff may hinder the usefulness of empagliflozin in the "real-world" HF population, and a more inclusive cutoff (eg, eGFR ≥30−45 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$) is probably more reasonable. Patients with Hb_{A1c} >10% should reach the 7%−10% levels considered for enrollment once adequate therapy is instituted. Likewise, 5% of those with Hb_{A1c} <7.0% may decompensate at 2-year follow-up.[4] Thus, it can be hypothesized that all patients with eGFR ≥30 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ and high CV risk with Hb_{A1c} >10% (3 patients in our cohort) and a few of those with Hb_{A1c} <7.0% (1 patient in our cohort) would be future candidates, totaling 21.0% of patients at 2-year follow-up. Finally, one might wonder whether patients with adequate control should

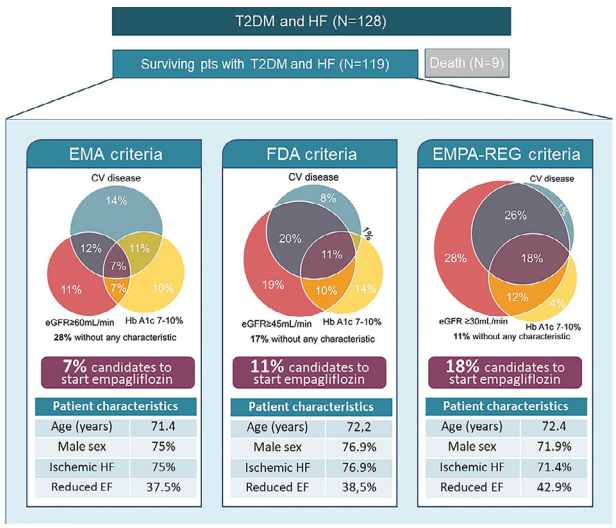

Fig. 1. Percentage of potential candidates to initiate empagliflozin and excluded patients according to EMPA-REG OUTCOME, European Medical Agency (EMA), and US Food and Drug Administration (FDA) criteria. Presence of high cardiovascular (CV) risk is illustrated in blue; estimated glomerular filtration rate (eGFR) in red; and Hb_{A1c} in yellow. T2DM, type 2 diabetes mellitus; HF, heart failure; EF, ejection fraction.

discontinue antidiabetic drugs with neutral CV effects to introduce empagliflozin.

Whether empagliflozin is effective in HF, regardless of DM, is being studied in EMPEROR-Reduced (NCT03057977) and EMPEROR-Preserved (NCT03057951). Additional challenges may have to be considered, especially adverse events related to polypharmacy and difficulty up-titrating currently well established disease-modifying drugs in HFrEF.[5]

The present study was limited by the single-center 1-year observational design. We did not investigate the possibility of using empagliflozin as a primary prevention strategy, presuming that the benefits of canagliflozin, as shown in CANVAS trial, are a sodium-glucose cotransporter 2 inhibitor class effect. The main finding is that, when considering "real-world" patients admitted for decompensated HF, a clinical event representative of a more advanced disease, only a minority shared the CV risk profile, Hb_{A1c}, and eGFR targets for inclusion in the EMPA-REG OUTCOME trial, limiting the extrapolation of the trial's observed CV benefits to the HF cohort.

Disclosures

None.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2019.02.002.

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References

1. Zinman B, Lachin JM, Inzucchi SE. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2016;374:1094.
2. Fonseca C, Araújo M, Moniz P, Marques F, Araújo I, Costa L, et al. Prevalence and prognostic impact of anemia and iron deficiency in patients hospitalized in an internal medicine ward: the PRO-IRON study. Eur J Haematol 2017;99:505–13.
3. Mahaffey KW, Neal B, Perkovic V, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin for primary and secondary prevention of cardiovascular events: results from the CANVAS program (Canagliflozin Cardiovascular Assessment Study). Circulation 2018;137:323–34.
4. McCoy RG, Ngufor C, van Houten HK, Caffo B, Shah ND. Trajectories of glycemic change in a national cohort of adults with previously controlled type 2 diabetes. Med Care 2017;55:956–64.
5. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Colvin MM, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation 2017;136:e137–61.

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