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Early treatment with a sodium-glucose co-transporter 2 inhibitor in high-risk patients with acute heart failure: Rationale for and design of the EMPA-AHF trial

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Aims The aim of the EMPA-AHF trial is to clarify whether early initiation of a sodium-glucose co-transporter 2 inhibitor before clinical stabilization is safe and beneficial for patients with acute heart failure (AHF) who are at a high risk of adverse events.

Methods The EMPA-AHF trial is a randomized, double-blind, placebo-controlled, multicentre trial examining the efficacy and safety of early initiation of empagliflozin (10 mg once daily). In total, 500 patients admitted for AHF will be randomized 1:1 to either empagliflozin 10 mg daily or placebo at 47 sites in Japan. Study entry requires hospitalization for AHF with dyspnoea, signs of volume overload, elevated natriuretic peptide, and at least one of the following criteria: estimated glomerular filtration rate <60 mL/min/1.73 m^2; already taking ≥40 mg of furosemide daily before hospitalization; and urine output of <300 mL within 2 hours after an adequate dose of intravenous furosemide. Patients will be randomized within 12 hours of hospital presentation, with treatment continued up to 90 days. The primary outcome is the clinical benefit of empagliflozin on the win ratio for a hierarchical composite endpoint consisting of death within 90 days, heart failure rehospitalization within 90 days, worsening heart failure during hospitalization, and urine output within 48 hours after treatment initiation.

Conclusion The EMPA-AHF trial is the first to evaluate the efficacy and safety of early initiation of empagliflozin in patients with AHF considered to be at high risk under conventional treatment. (Am Heart J 2023;257:85–92.)

Acute heart failure (AHF) is a leading cause of hospitalization worldwide, and is associated with high mortality and morbidity.[1-3] While novel therapeutic interventions for AHF have been tested in randomized controlled trials, no treatment has demonstrated improvement in clinical outcomes.[4-7] Consequently, intravenous diuretics have been the mainstay of treatment for decades.[8] The prognosis of patients with AHF remains unacceptably poor, and previous studies have indicated that specific subgroups, such as those with impaired renal function, requiring hospitalization due to worsening heart failure (WHF) despite being on heart failure medications, and those who do not respond well to diuretic therapy provided in the acute phase, are particularly at high risk of adverse events.[9-12] However, most previous clinical trials have not specifically targeted this population, and currently, the treatment strategy for those at high risk under conventional treatment is not significantly different from that for those who are not at high risk.

Sodium-glucose co-transporter 2 inhibitors (SGLT2is), which were initially developed as antihyperglycemic drugs, have been shown to reduce the risk of heart

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failure hospitalization in patients with type 2 diabetes, and also improve the prognosis of patients with heart failure regardless of the coexistence of diabetes.[13-17] The positive impact of SGLT2i on prognosis was consistently observed in patients with heart failure with reduced and preserved ejection fraction.[15,17] Moreover, subsequent post-hoc analyses of these trials have demonstrated that treatment with SGLT2is was associated with reduction in the risk of cardiovascular death, hospitalization for heart failure or an emergent/urgent heart failure visit shortly after treatment initiation.[18,19] These findings suggest the possibility that early initiation of SGLT2i therapy, particularly early after hospitalization for AHF, is clinically beneficial. Indeed, 2 large-scale, double-blinded, randomized controlled trials consistently showed the efficacy and safety of introducing SGLT2is during hospitalization or early after discharge in hospitalized patients with AHF.[20,21] However, these trials enrolled patients after they were clinically stabilized with the conventional treatment and not necessarily in a very acute phase. Therefore, the question of whether SGLT2is can be a safe and effective additional treatment for patients with AHF in the very early phase of admission, has yet to be answered. Therefore, we designed the EMPA-AHF trial to clarify whether initiating empagliflozin in the very acute phase of admission is safe, and clinically and prognostically beneficial in high-risk patients with AHF.

Study design

Trial structure and oversight

The EMPA-AHF trial is a multicentre, randomized, double-blind, placebo-controlled trial designed to evaluate the efficacy and safety of early initiation of once-daily oral empagliflozin 10 mg in patients hospitalized for AHF. The trial has been registered at ClinicalTrials.gov (NCT05392764), and is being conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. This study has been reviewed and approved by the IRB of Nihon University Itabashi Hospital. The EMPA-AHF trial will be conducted at 47 university and community hospitals in Japan. All participants will provide written informed consent prior to study entry. Funding for the EMPA-AHF trial was provided by Nippon Boehringer Ingelheim Co., Ltd and Eli Lilly Japan K.K. under a research agreement with Juntendo University. The study was designed jointly with an executive committee consisting of academic members and representatives of Nippon Boehringer Ingelheim. The primary and secondary outcomes are adjudicated by an independent adjudication committee, and adverse events are monitored by an independent safety monitoring committee. Each committee consists of three judges who are blinded to the treatment arm. The members of the committees are listed in Supplemental Table S1. Patient enrollment began in September 2022, when the first patient was randomized, and is scheduled to be completed in March 2024.

Study participants

Patients who meet all the inclusion criteria and do not meet any of the exclusion criteria will be enrolled in the study (Table 1 and Figure).

Key inclusion criteria are as follows: (1) age ≥20 and <90 years; (2) hospitalized with a diagnosis of AHF, requiring intravenous loop diuretic therapy, with all of the following characteristics: (i) dyspnoea at rest or induced by slight exertion, (ii) at least two of the following findings: jugular venous distention, pulmonary rales, lower leg oedema, and pulmonary congestion on chest X-ray, and (iii) brain natriuretic peptide (BNP) ≥350 pg/mL or N-terminal (NT)-proBNP ≥1,400 pg/mL if sinus rhythm present at the time of admission, or BNP ≥500 pg/mL or NT-proBNP ≥2,000 pg/mL if atrial fibrillation present at the time of admission; (3) at least one of the following characteristics: (i) estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, as calculated using the CKD Epidemiology Collaboration for Japanese,[22] (ii) already taking ≥40 mg of oral furosemide during the period before hospitalization, (iii) urine output of <300 mL during the 2 hours following an appropriate dose of intravenous furosemide administered after hospitalization. An appropriate dose of intravenous furosemide is 20 mg for patients who have not been taking furosemide regularly before hospitalization, and is the same as, or greater than, the daily oral dose for patients who have been taking furosemide regularly before hospitalization (eg, oral furosemide 40 mg BID = adequate dose of intravenous furosemide 80 mg or more)[8,23]; and (4) provided written consent to participate in the study.

Key exclusion criteria are as follows: eGFR <20 mL/min/1.73 m^2 at the time of admission, already taking a SGLT2i within 3 months prior to hospitalization; type 1 diabetes mellitus; systolic blood pressure <90 mmHg; expected to newly require treatment with thiazide, tolvaptan, or carperitide within 48 hours after hospitalization; main cause of heart failure exacerbation is not fluid retention, acute coronary syndrome, pulmonary thromboembolism, or a cerebrovascular accident is the main cause of the present hospitalization; and risk of ketoacidosis or hyperosmolar hyperglycaemia. Patients on intravenous inotropes, vasopressors, and/or vasodilators are not excluded if blood pressure is >90 mmHg at enrollment. Patients with new ACS, cerebral infarction, or transient ischemic attack are not included, even if these conditions are not the primary cause of AHF. Full inclusion and exclusion criteria are provided in Supplemental Tables S2 and S3.

Patients will be randomized within 12 hours of hospital presentation, and study treatment will be started as soon as possible, with a time limit of 18 hours from randomization to treatment initiation. Treatment for AHF other

Table 1. Key inclusion and exclusion criteria

Key inclusion criteria

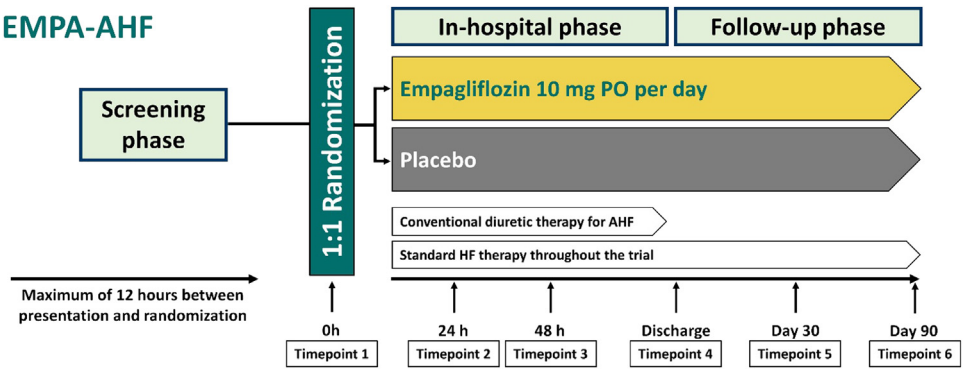
1. Age of ≥20 and <90 years
2. Hospitalized with a diagnosis of acute heart failure, requiring intravenous loop diuretic therapy, with all of the following characteristics:
   i) Dyspnoea at rest or induced by slight exertion
   ii) At least two of the following findings: jugular venous distention, pulmonary rales, lower leg oedema, and pulmonary congestion on chest X-ray
   iii) If the patient has a sinus rhythm at the time of admission, BNP ≥350 pg/mL or NT-proBNP ≥1,400 pg/mL; if the patient has atrial fibrillation at the time of admission, BNP ≥500 pg/mL or NT-proBNP ≥2,000 pg/mL
3. At least one of the following characteristics:
   i) eGFR <60 mL/min/1.72 m^2
   ii) Already taking ≥40 mg of oral furosemide during the period before hospitalization
   iii) Urine output of <300 mL during the 2 hours following an adequate dose of intravenous furosemide
4. Provided written consent to participate in the study

Key exclusion criteria

1. eGFR <20 mL/min/1.73 m^2 at the time of admission
2. Already taking a SGLT2i within 3 months prior to hospitalization
3. Type 1 diabetes mellitus
4. Systolic blood pressure <90 mmHg
5. Expected to newly require treatment with thiazide, tolvaptan, or carperitide within 48 h after hospitalization
6. Main cause of acute heart failure hospitalization is not fluid retention (eg, persistent ventricular tachycardia, persistent atrial fibrillation/atrial flutter with a ventricular response rate of ≥130 bpm, persistent bradycardia with a ventricular response rate of <45 bpm, an infection, severe anaemia, and an acute exacerbation of COPD)
7. Acute coronary syndrome, pulmonary thromboembolism, or a cerebrovascular accident is the main cause of the present hospitalizationAt risk of ketoacidosis or hyperosmolar hyperglycaemia
8. At risk of ketoacidosis or hyperosmolar hyperglycaemia

BNP, brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

Figure



Study flow chart Patients will be randomized to either the empagliflozin or placebo group within 12 hours of hospital presentation. Treatment for AHF other than a SGLT2i is performed at the discretion of the physician responsible for the patient. After randomization, patients will be evaluated at 24 and 48 h after treatment initiation and at hospital discharge. After hospital discharge, patients complete regularly scheduled visits at the study site at 30 and 90 days after treatment initiation. The occurrence of efficacy endpoints and adverse events will be assessed at each timepoint. AHF, acute heart failure; SGLT2is, sodium-glucose co-transporter 2 inhibitor.

than a SGLT2i will be performed at the discretion of the physician responsible for the patient.

Study visits and follow-up

Screening for the study will start when patients present to the hospital, and informed consent will be obtained prior to study entry (Figure). Patients will be subsequently randomized (Timepoint 1) to double-blind treatment using a web-based randomization system, with a 1:1 ratio to either the empagliflozin or placebo group. After randomization, patients will be evaluated at 24 (Timepoint 2) and 48 hours (Timepoint 3) after treatment initiation and at hospital discharge (Timepoint 4). After hospital discharge, the patient will visit the study

Table 2. Primary and key secondary outcomes*

Primary outcome

- A hierarchical composite endpoint consisting of death within 90 days, heart failure rehospitalization within 90 days, WHF during hospitalization, and urine output up to 48 hours after treatment initiation, assessed by the win ratio

Key secondary outcomes

- A hierarchical composite endpoint consisting of death within 90 days, heart failure readmission within 90 days, and WHF during hospitalization
- A composite endpoint consisting of WHF during hospitalization, death, heart failure rehospitalization, urgent visit for WHF, intensification of diuretic therapy, and worsening NYHA class within 90 days*
- Change in NT-proBNP from randomization to 48 hours
- Diuretic response to intravenous furosemide 40 mg at 48 hours after treatment initiation
- Improvement in KCCQ-TSS of ≥5 points from randomization to 30 and 90 days after treatment initiation

* Worsening NYHA class is defined as worsening of NYHA at 30 and 90 days follow up compared to NYHA at discharge.HF, heart failure; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire total symptom score; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; WHF, worsening heart failure.

site for regularly scheduled visits at 30 (Timepoint 5) and 90 days (Timepoint 6) after treatment initiation. Detailed schedules and assessments are provided in Supplemental Table S4. These on-site visits will assess the occurrence of efficacy end points and adverse events, and include evaluations of symptoms (dyspnoea, New York Heart Association [NYHA] class, and Kansas City Cardiomyopathy Questionnaire [KCCQ]), laboratory data (NT-proBNP, eGFR, and cardiac troponin), and echocardiography data.

Primary win ratio outcome

The primary outcome of the EMPA-AHF trial is the clinical benefit of empagliflozin as assessed by the win ratio for a hierarchical composite end point consisting of death within 90 days, heart failure rehospitalization within 90 days, WHF during hospitalization, and urine output within 48 hours after treatment initiation, considered in this order (Table 2).[24] We will use the unmatched all possible pair approach to the win ratio calculation.[24] The win/lose status for the 90-day death outcome will be based on time-to-death within the 90-day assessment window. A tie for the death outcome will occur when neither experience death within 90 days, censoring occurs before the comparator dies, or two deaths occur on the same day. In case of a tie, heart failure rehospitalization will be assessed based on time-to-heart-failure-rehospitalization within the 90-day assessment window. When there is a tie for the heart failure rehospitalization outcome, WHF will be assessed based on time-to-worsening during hospitalization. When there is a tie for WHF outcome, a greater urine output will determine the win/lose status.

The definition of each outcome is the following. Heart failure rehospitalization is defined as a hospital admission due to a primary diagnosis of heart failure with new or worsening symptoms and objective evidence of heart failure, requiring an intensification of treatment. WHF during hospitalization is defined as new or worsening symptoms and objective evidence of heart failure, requiring intensification of therapy after the stabilization of hemodynamic status under initial therapies during the indexed hospitalization. The stabilization of hemodynamic status is defined as meeting all of the following requirements: (1) systolic blood pressure ≥100 mmHg for 6 hours and no symptoms of hypotension; (2) no use of intravenous diuretics for 24 hours; (3) no use of intravenous vasodilators for 24 hours; and (4) no use of intravenous inotropic agents for 24 hours.

Secondary outcomes

Key secondary outcomes are as follows (Table 2): (1) the win ratio for a hierarchical composite end point consisting of death within 90 days, heart failure readmission within 90 days, and WHF during hospitalization; (2) a composite endpoint consisting of WHF during hospitalization, death, heart failure rehospitalization, urgent visit for WHF, intensification of diuretic therapy, and worsening NYHA class within 90 days; (3) change in NT-proBNP level from randomization to 48 hours; (4) diuretic response, calculated as the urine output achieved by loop diuretics (40 mg intravenous furosemide-equivalent dose) at 48 hours after treatment initiation; and (5) improvement in KCCQ-total symptom score (KCCQ-TSS) of ≥5 points from randomization to 30 and 90 days after treatment initiation. Additional secondary outcomes planned for analysis are provided in Supplemental Table S5. The win ratio will be used to analyse the hierarchical composite endpoint. The analyses will follow the intention-to-treat principle, assigning the patient to treatment groups as randomized.

Adverse events of special interest include liver dysfunction, renal dysfunction, metabolic acidosis, ketoacidosis, diabetic ketoacidosis, and lower limb amputation.

Sample size calculation

As our primary endpoint was based on win ratio, we used a simulation-based approach to sample size calculation. We generated 10,000 simulated trials with a given

sample size and randomly assigned subjects to the treatment arms with a 1:1 ratio. The 90-day rates of untreated outcomes were assumed to be 0.093 for death, 0.103 for heart failure hospitalization, and 0.077 for worsening heart failure during hospitalization based on the literature.[25-28] We further introduced correlation among these time-to-event outcomes using a shared gamma frailty variable.[29,30] The protective treatment effect for each time-to-event variable was assumed to be 10%.[15,31] For the urine output outcome, the minimum between-group difference in clinically significant urine volume was assumed to be 1,000 mL/d.[31] The win ratio assessment in each simulated trial used the R WinRatio package, which accommodates both time-to-event and continuous outcomes.[32] The number of simulated trials that gave significant results divided by 10,000 represents the power at the given sample size. With a 2-sided significance level of 5%, a total sample size of 440 achieved the and a target statistical power of 90% to detect differences in the endpoint variables, the total required sample size was calculated as 440. Assuming a dropout rate of 12%, the required sample size was finally calculated as 500, which will be randomly assigned to either group at a 1:1 ratio. Full details of the power calculations are presented in Supplemental Table S6.

Discussion

The EMPA-AHF trial is the first to evaluate the efficacy and safety of the early initiation of empagliflozin (10 mg) in patients with AHF expected to be at high risk when treated with conventional therapy. The results of this study will provide invaluable information regarding the important and clinically relevant question, whether a modification of the treatment strategy early after hospital presentation with empagliflozin for high-risk patients with AHF impacts their clinical course.

There are 3 characteristics that render the EMPA-AHF trial unique among trials on the use of SGLT2is in patients with AHF. Firstly, SGLT2i therapy will be initiated at an early phase (specifically, before clinical stabilization) in the EMPA-AHF trial. In contrast, 2 recent randomized controlled, double-blinded studies tested the efficacy and safety of SGLT2is in patients hospitalized for AHF who were clinically stabilized with conventional treatment.[20,21] In the SOLOIST-WHF study, sotagliflozin or placebo was introduced, either before or within 3 days of discharge, to patients with type 2 diabetes who required hospitalization due to heart failure exacerbation;[21] treatment with sotagliflozin was associated with a lower incidence of the composite event of death from cardiovascular causes and hospitalizations and urgent visits for heart failure. In the EMPULSE study, empagliflozin was introduced following stabilization between 24 hours and 5 days after admission, and showed a clinical benefit, as evaluated by a hierarchical composite end point of death, heart failure events, and change in KCCQ-TSS.[20] DAPA ACT HF-TIMI 68 is an ongoing randomized, double-blind, placebo-controlled trial evaluating the efficacy of in-hospital initiation of dapagliflozin on the clinical outcome of cardiovascular death or worsening heart failure in patients hospitalized for AHF (NCT04363697). In this trial, dapagliflozin is also initiated after hemodynamic stabilization and no earlier than 24 hours. These studies required patients to be stabilized by conventional treatment without SGLT2is, or to have completed AHF treatment and be ready for discharge. Therefore, the impact of initiating SGLT2i therapy within the very early phase of hospitalization, particularly before clinical stabilization, has not yet been clarified. Because patients with AHF are considered to suffer congestion-induced organ damage immediately after hospitalization,[25, 33] prompt initiation of the treatment may ameliorate multiple organ damage and consequently improve the prognosis.[25] In this context, the EMPA-RESPONS-AHF study preliminarily evaluated the safety and clinical efficacy of early empagliflozin therapy in 79 patients with AHF randomized to treatment with empagliflozin (10 mg) or placebo once daily within 24 hours of hospital presentation.[31] Although the empagliflozin group did not show superiority in the predefined primary outcomes of change in dyspnoea, diuretic response, NT-proBNP level, and length of hospital stay, treatment with empagliflozin was associated with an increase in urine output and a lower incidence of the composite endpoint of WHF during hospitalization, rehospitalization for heart failure, and death within 60 days, without an association with adverse events. While this previous study supports the benefit of early empagliflozin therapy, interpretation of the study results requires caution given the limited number of events and study sample size. The EMPAG-HF trial randomized patients with AHF within 12 hours of admission and reported that empagliflozin increased urine output up to 5 days after admission.[34] However, this trial enrolled a relatively small number of patients ($n = 60$), had a short intervention period of 5 days, and did not evaluate clinical outcomes such as mortality, HF readmission, and in-hospital WHF as the primary or secondary end points. The ongoing DICTATE-AHF trial is open-label, randomized study evaluating the efficacy and safety of early initiation of dapagliflozin 10 mg once daily within 24 hours of presentation in 240 patients with AHF. The study enrolls patients with and without diabetes, and the primary endpoint is diuretic response but not clinically more important events such as death or heart failure rehospitalization.[35] The detailed comparison of EMA-AHF and DICTATE-AHF is shown in Table 3. Against this backdrop, the EMPA-AHF trial is expected to provide novel insights into the role of empagliflozin in patients with AHF with or without diabetes, as it is the first well-powered study targeting patients early after hospital presentation and before stabilization with conventional

Table 3. EMPA-AHF and DICTATE-AHF trials

	EMPA-AHF	DICTATE-AHF
Study population	Patients hospitalized for AHF	Patients hospitalized for AHF
Number of patients	500	240
Randomization	Within 12 hours of hospital presentation	Within 24 hours of hospital presentation
Key differences in inclusion and exclusion criteria	Includes patients with signs of volume overload requiring intravenous loop diuretic therapy **and** at least one of the following characteristics: estimated glomerular filtration rate <60 mL/min/1.73 m^2; already taking ≥40 mg of furosemide daily before hospitalization; and urine output of <300 mL within 2 hours after an adequate dose of intravenous furosemide Patients requiring intravenous inotropes and/or vasopressors are *not* excluded as long as systolic blood pressure is ≥ 90 mmHg	Includes patients with signs of volume overload requiring intravenous loop diuretic therapy Patients requiring intravenous inotropic therapy are excluded
Key differences in interventions	Empagliflozin 10 mg per day and diuretic therapy vs placebo and diuretic therapy Diuretic therapy is based on each physician's discretion	Dapagliflozin 10 mg per day and diuretic therapy vs. diuretic therapy Diuretic therapy is protocolized
Treatment duration	90 days	5 days or until hospital discharge
Difference in outcomes	Primary outcome: A hierarchical composite endpoint consisting of death within 90 days, heart failure rehospitalization within 90 days, WHF during hospitalization, and urine output up to 48 hours after treatment initiation, assessed by the win ratio Evaluates time to hemodynamic stabilization as part of the secondary outcomes	Primary outcome: Cumulative change in weight from baseline to day 5 or discharge if earlier
Differences in study questions and evidence gaps to be addressed	To evaluate whether early initiation of empagliflozin before clinical stabilization is safe and beneficial for patients with AHF who are at a high risk of adverse events	To evaluate whether early initiation of dapagliflozin facilitates decongestion in patients with AHF

treatment. Moreover, the EMPA-AHF trial will not exclude those who cannot achieve clinical stabilization by conventional therapy, that is, the subgroup excluded in previous studies investigating the role of SGLT2i therapy in patients hospitalized for AHF.[20,21,36]

Secondly, the EMPA-AHF trial targets patients with AHF considered at high risk when treated with the conventional treatment strategy. Although immediate intervention is associated with an improvement in congestion, and is considered to alleviate organ damage,[4,5] no specific drug has been shown to improve the prognosis of patients with AHF, and treatment still predominantly relies on diuretics. Accordingly, treatment options tailored according to the risk of adverse events in individual patients are lacking. In the EMPA-AHF trial, patients with AHF considered to be at high risk under conventional treatment are defined as those who meet at least one of the following three criteria: renal dysfunction at the time of admission[9]; hospitalization with excessive fluid volume required despite being treated with oral diuretics[10]; and poor response to the initial recommended dose of intravenous loop diuretics.[37] Although numerous studies have shown that a poor response to loop diuretics is strongly associated with a poor prognosis,[11,12] no therapy has been shown to be safe and effective in this population, and the latest statement only recommends increasing the dose of loop diuretics or combination diuretic therapy.[38] Empagliflozin inhibits the reuptake of glucose and sodium in the proximal tubules,[39] and has been reported to intensify sodium excretion when used together with loop diuretics.[40] Another unique property of empagliflozin is osmotic diuresis via glucose excretion, which may specifically decrease tissue congestion and mitigate organ damage.[41] These features can be advantageous, particularly for those not responding well to conventional treatment strategies using mainly loop diuretics.

Lastly, the primary end point in EMPA-AHF is defined as a hierarchical composite end point of death, heart failure readmission, WHF during hospitalization, and urine output after treatment initiation, with the more important end points listed in order from death. In previous studies using a composite end point, each component was weighted equally and only the earliest event was used, and the clinical course after the earliest event was ignored. However, this approach fails to take into account the order of the clinical importance of each event, and ignores fatal events that occur after non-fatal events. In contrast, the win ratio assigns a random pair of patients in the treatment and placebo groups and determines a winner and loser based on which of the 2 patients has the most clinically significant event first (ie, 90-day mortality in the EMPA-AHF trial).[29,42] If neither patient has an event, it is considered a tie. The process is repeated sequentially for the next important outcome (ie, heart failure rehospitalization, followed by WHF during hos-

pitalization and urine output in the EMPA-AHF trial). Finally, the win ratio is calculated from the ratio of winners to losers for all end points. Thus, clinical outcomes such as death are assessed with greater emphasis, while "soft" end points such as urine output or patient-centred outcomes (eg, change in KCCQ score) are evaluated simultaneously.[20] Another advantage of using the win ratio is that pairwise comparisons can be used without the need for the proportionality of hazards. Pathophysiological variables and patient-oriented outcomes are usually quantitative. Including these measures in the hierarchical outcomes of the win ratio helps identify a winner or a loser in most pairwise comparisons due to their variable distribution. This may significantly increase the statistical power of the win ratio approach.[29] Indeed, some ongoing clinical trials take this advantage and include biomarkers such as BNP and patient-oriented outcomes such as KCCQ in the hierarchical outcomes of the win ratio.[43,44]

In EMPA-AHF, WHF is defined as the worsening of HF after hemodynamic stabilization, which requires no use of intravenous diuretics, inotropes, and vasodilators for 24 hours. Therefore, the efficacy and safety of empagliflozin immediately after its initiation may not be captured by the endpoint of WHF in EMPA-AHF. To address this issue, we employ time to hemodynamic stabilization as a secondary end point. This is a unique end point because previous trials have enrolled patients after hemodynamic stabilization, and, therefore, this end point can reflect the very early effect of empagliflozin.

Urine output is evaluated as a part of the primary outcome in EMPA-AHF. The effect of empagliflozin on urine output can be influenced by the diuretic dosage. However, previous randomized controlled trials have reported that empagliflozin increases urine output without adjustment for diuretic dosage.[31,34,36] Urine output is a simple and clinically important measure; thus, it is a reasonable component to be used in the primary composite end point. We also evaluate the diuretic response as a secondary end point to adjust the influence of the dosage of loop diuretics on urine output.

Conclusion

The EMPA-AHF trial will evaluate the efficacy and safety of initiating empagliflozin in the acute phase before clinical stabilization in high-risk patients with AHF. This study may provide invaluable information for optimizing treatment according to risk stratification in patients with AHF.

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Conflict of Interest

Y.H. received an honorarium from Otsuka Pharmaceutical Co, Novartis Japan, AstraZeneca, and Nippon Boehringer Ingelheim Co., Ltd. Y. M. received an honorarium from Otsuka Pharmaceutical Co, Novartis Japan, Bayer Inc., and AstraZeneca, and collaborative research grant from Pfizer Japan Inc., Otsuka Pharmaceutical Co and EN Otsuka Pharmaceutical Co., Ltd. D.N. is an employee of Nippon Boehringer Ingelheim Co. Ltd. K.D. received speaker fees from Abbott, Astra Zeneca and Boehringer Ingelheim. K.Y. received consulting fees from OM1, Inc for unrelated projects. A.A.V. has received research support and/or has been a consultant for Amgen, AstraZeneca (AZ), Bayer AG, Boehringer Ingelheim (BI), Cytokinetics, Merck, Myokardia, Novo Nordisk (NN), Novartis, and Roche Diagnostics. Other authors have no conflict of interest to declare.

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None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2022.12.005.

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