Eligibility for Dapagliflozin and Empagliflozin in a Real-world Heart Failure Population

TONJE THORVALDSEN, MD, PhD,[1,2,†] GIULIA FERRANNINI, MD,[1,†] LINDA MELLBIN, MD, PhD,[1,2] LINA BENSON, MSc,[1] FRANCESCO COSENTINO, MD PhD,[1,2] JOHN J.V. MCMURRAY, MD,[3] ULF DAHLSTRÖM, MD, PhD,[4] LARS H. LUND, MD, PhD,[1,2,#] AND GIANLUIGI SAVARESE, MD, PhD[1,2,#]

Stockholm, and Linköping, Sweden; and Glasgow, UK; and the

ABSTRACT

Background: We investigated eligibility for dapagliflozin and empagliflozin in a real-world heart failure (HF) cohort based on selection criteria of 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), and EMPEROR (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction and Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with APreserved Ejection Fraction) trials.

Methods and Results: Selection criteria were applied to the Swedish HF registry outpatient population according to 3 scenarios: (i) a "trial scenario" applying all selection criteria; (ii) a "pragmatic scenario" applying the most clinically relevant criteria; and (iii) a "label scenario" following the regulatory agencies labels. Of the 49,317 patients, 55% had an ejection fraction of less than 40% and were assessed for eligibility based on DAPA-HF and EMPEROR-Reduced, 45% had ejection fraction of 40% or greater and were assessed based on EMPEROR-Preserved and DELIVER. Eligibility using trial, pragmatic, and label scenarios was 35%, 61%, and 80% for DAPA-HF; 31%, 55%, and 81% for EMPEROR-Reduced; 30%, 61%, and 74% for DELIVER; and 32%, 59%, and 75% for EMPEROR-Preserved, respectively. The main selection criteria limiting eligibility were HF duration and N-terminal pro-B type natriuretic peptide levels. Eligible patients had more severe HF, more comorbidities, higher use of HF treatments and higher mortality and morbidity.

Clinical Highlights: Large clinical trials for the approval of new drugs in heart failure often apply numerous selection criteria, limiting the generalizability of trial findings to real-world populations. We assessed eligibility for dapagliflozin and empagliflozin according to trial criteria, the more practical criteria usually applied in daily practice for treatment selection, and the criteria mandated by regulatory agencies, in a real-word heart failure population. Our results from the Swedish Heart Failure Registry show that a great number of patients with heart failure might be candidates for these therapies, which have been shown to significantly decrease morbidity and mortality; therefore, their use should be implemented in clinical practice.

Lay summary: When strictly applying selection criteria used in clinical trials, only one-third of a real-world heart failure population is eligible for treatment with empagliflozin and dapagliflozin. Adopting approaches that consider the most meaningful criteria, that is, those most clinically relevant or those mandated by regulatory agencies, significantly broadened eligibility.

From the [1]From the Unit of Cardiology, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden; [2]Heart and Vascular Theme, Karolinska University Hospital, Stockholm, Sweden; [3]British Heart Foundation, Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK; and the and [4]Department of Cardiology and Department of Health, Medicine and Caring Sciences, Linköping University, Linköping, Sweden.

Manuscript received December 20, 2021; revised manuscript received April 7, 2022; revised manuscript accepted April 8, 2022.

Reprint requests: Gianluigi Savarese, MD, PhD, Division of Cardiology, Department of Medicine, Karolinska Institutet, Eugeniavägen 27, S1:02, 171 76 Stockholm, Sweden, Tel: +46 (0)76 4165215; Fax: +46(0)8344964. E-mail: gianluigi.savarese@ki.se

Supported by AstraZeneca (support to Dr. Savarese's institution), and Boehringer Ingelheim (support to Dr. Lund's institution). The funding sources had no role in the design of this study, execution, analyses, interpretation of the data, or decision to submit results.

†These authors equally contributed as first authors.

#These authors equally contributed as last authors.

See page 1060 for disclosure information.

1071-9164/$ - see front matter

https://doi.org/10.1016/j.cardfail.2022.04.011

These results might contribute to future trial design taking into consideration the characteristics of real-world populations, feasibility, and potential cost benefits.
Conclusions: In a real-world HF setting, eligibility for sodium glucose co-transporter-2 inhibitors was similar whether selection criteria from DAPA-HF or EMPEROR-Reduced were applied in HFrEF, or EMPEROR-Preserved or DELIVER in HFpEF. These data might help stakeholders assessing the consequences of future trial eligibility. (*J Cardiac Fail 2022;28:1050−1062*)
Key Words: Heart failure, Eligibility, SGLT2 inhibitors, SwedeHF.

Large cardiovascular outcome trials enrolling patients with type 2 diabetes showed that sodium glucose co-transporter-2 inhibitors (SGLT2i) substantially decreased heart failure (HF) hospitalization, both in patients with or without a history of HF.[1−8] This finding was hypothesis-generating for randomized controlled trials (RCTs) testing the SGLT2i dapagliflozin and empagliflozin in patients with HF regardless of comorbid diabetes. Among these, DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) and EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction) demonstrated the efficacy of dapagliflozin and empagliflozin, respectively, for the reduction of cardiovascular death/HF hospitalization in patients with HF with reduced ejection fraction (HFrEF) regardless of type 2 diabetes status.[9,10] Later, the EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction) trial showed that empagliflozin decreased the risk of cardiovascular death/HF hospitalization also in patients with EF above 40%, either with or without diabetes.[11] The ongoing DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure)[12] trial is testing dapagliflozin in patients with HF with mildly reduced and preserved EF (EF of >40%), with or without type 2 diabetes, with a primary composite endpoint of cardiovascular death and hospitalization or urgent visit for HF. The SOLOIST-WHF (Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure) demonstrated that the SGLT1-2 inhibitor sotagliflozin decreased cardiovascular death and HF hospitalization in patients with type 2 diabetes who were recently hospitalized for worsening HF, regardless of the EF.[13] Finally, the EMPULSE (Empagliflozin in Patients Hospitalized for Acute Heart Failure) trial showed that empagliflozin had better clinical benefit compared with placebo in patients with a primary diagnosis of acute de novo or decompensated chronic HF regardless of EF.[14]

RCTs apply selection criteria to ensure the diagnosis of HF and to enrich for modifiable cardiovascular events. Therefore, trials generally enroll patients with lower noncardiovascular risk. However, these criteria may limit the generalizability (external validity) of the trial findings and be reflected in regulatory approval and labelling, guideline recommendations, reimbursement criteria, and clinical acceptance and implementation of novel interventions.

Therefore, in a real-world cohort of patients with HF, we investigated the proportion of patients eligible for dapagliflozin/empagliflozin based on the inclusion and exclusion criteria used in DAPA-HF and EMPEROR-Reduced, which were positive in HFrEF; EMPEROR-Preserved, which was positive in HFmrEF/HFpEF; and DELIVER in the possibility that this will also be positive, as well as the characteristics and the outcomes of patients fulfilling or not fulfilling the eligibility criteria.

Methods

Data Sources

Data from the Swedish HF Registry (SwedeHF) from May 2000 to December 2018 were analyzed. SwedeHF was linked with the National Patient Registry, Statistics Sweden, and the Cause of Death Registry by the personal identification number, which all residents in Sweden have regardless of citizenship.

SwedeHF has been described previously.[15] It is an ongoing quality registry founded in 2000. Most Swedish hospitals enroll patients (approximately 60 of 75), and approximately 80 variables are recorded from adult inpatient wards and outpatient clinics (www.swedehf.se). The inclusion criterion is clinician-judged HF, regardless of EF, thus including HFrEF, HF with mildly reduced EF (HFmrEF), and HF with preserved EF (HFpEF), with approximately 55% of patients with an EF of less than 40% (HFrEF), 22% with an EF of 40%−49% (HFmrEF), and 23% with an EF of 50% or greater (HFpEF).[16]

The National Patient Registry (NPR) is a national mandatory registration of administrative records maintained by The Swedish Board of Health and Welfare (www.socialstyrelsen.se). NPR collects *International Classification of Diseases* diagnostic and procedure codes reported by clinicians in the medical record. The positive predictive value for most diagnoses ranges between 85% and 95%.[17] We used the NPR for additional baseline comorbidities

not available in SwedeHF and the hospitalization outcomes.

Statistics Sweden (www.scb.se) provides socioeconomic data such as income, level of education, marital status, and living arrangements. The Cause of Death Registry provides the date and cause of death.

SwedeHF and the present study, as well as the linkage of all these data sources, were approved by a multisite ethics committee. Individual patient consent in SwedeHF is not required, but patients are informed on the entry in national quality registries and allowed to opt out.

Eligibility for Dapagliflozin and Empagliflozin

In SwedeHF, EF is recorded as a categorical variable as follows: less than 30%, 30%−39%, 40%−49%, and 50% or greater. Therefore, patients in SwedeHF were considered potentially eligible, and thus included in the denominator for the eligibility rates calculation, if they were outpatients and had an EF of less than 40% for DAPA-HF and EMPEROR-Reduced analyses, and if they were outpatients and had an EF of 40% or greater for EMPEROR-Preserved and DELIVER. For patients with multiple registrations, the most recent visit was selected, assuming that it would be the most representative of the current clinical status and care.

All 4 trials required stable HF for inclusion, that is, DAPA-HF, EMPEROR-Reduced, and EMPEROR-Preserved included only outpatients. In DELIVER, inpatients could be enrolled if they had been off intravenous diuretics for more than 24 hours. Because intravenous diuretic administration was not recorded in SwedeHF, we only used outpatients in our analyses for all 4 trials.

For each trial, 3 scenarios were considered for eligibility rates calculation: (i) a "trial scenario" where all the inclusion/exclusion criteria from the trials which could be assessed in our dataset were applied, (ii) a "pragmatic scenario," and (iii) a "label scenario." In the pragmatic scenario, we considered the inclusion and exclusion criteria most likely to determine the use of SGLT2i in clinical practice, namely, age, New York Heart Association (NYHA) functional class, levels of N-terminal pro-B type natriuretic peptide (NT-proBNP), hypotension, renal function, and type 1 diabetes mellitus. Selection criteria considered for the pragmatic scenario are marked with an asterisk in Tables 1 and 2 and in Supplemental Tables 6 and 7. As regards the label scenario, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) label for dapagliflozin considers NYHA functional classes II−IV with the exclusion of type 1 diabetes, patients on dialysis and patients with an estimated glomerular filtration rate (eGFR) of less than 25 mL/min/1.73 m^{2}. We applied the same approach and criteria for empagliflozin in HFrEF/HFpEF, but with the EF and eGFR as defined in the respective trial protocols (inclusion criteria: EF $\leq$40% in EMPEROR-Reduced and EF$>$40% in EMPEROR-Preserved) and with the exclusion of eGFR of less than 20 mL/min/1.73 m^2 as per EMA/FDA label. Selection criteria used in the label scenario are showed in Supplemental Table 5. Because not all data required for defining the inclusion and exclusion criteria were available in SwedeHF, a few selection criteria could not be applied or were applied only by using slightly different definitions or surrogates.

All the original inclusion and exclusion criteria from the trials[12,18−20] and the corresponding definitions in SwedeHF are reported in Supplemental Tables 1−4.

Statistical Analyses

Eligibility calculations were reported as frequencies (percentages) and represent the remaining cohort after applying the respective inclusion/exclusion criteria. The criteria were not ordered.

Baseline characteristics were reported as frequencies (percentages) for categorical and as median (interquartile range) for continuous variables. Comparison in eligible vs non-eligible patients was assessed by Wilcoxon Mann−Whitney *U* test for continuous and the χ^2 test for categorical variables. Incidence rates (per 100 patient-years) for all-cause, cardiovascular, and noncardiovascular mortality, HF hospitalization, and the composite of cardiovascular mortality and HF hospitalization were calculated and compared in eligible vs non-eligible patients by Poisson regression models where time was included as an offset.

Some of the variables used for eligibility assessment had missing data. For the main analysis, missing data were handled by single imputation (STATA command mi impute). Two consistency analyses were performed: (1) only patients with available entries for the variable needed for the eligibility assessment were considered (ie, complete-case analysis); and (2) patients with missing entries for variables needed for eligibility assessment were considered as fulfilling eligibility criteria, that is, missing as eligible (Supplemental Tables 6−7). Variables used in the imputation model are marked with an asterisk in Supplemental Table 8.

For all the analyses, the level of significance was set to 5%, 2 sided, and Stata software version 16.0 was used.

Results

Between May 11, 2000, and December 31, 2018, there were 156,544 registrations in SwedeHF. Of

these, 89,603 were registrations as outpatients, out of which 77,928 had a reported EF. After excluding multiple registrations per patient, 49,317 unique patients were considered for analyses, 55% (26,887) with an EF of less than 40% and 45% (22,430) with an of EF 40% or greater (with 45% of these having an of EF 50% or greater). In the groups of patients with an EF of less than 40% and an of EF 40% or greater, 27% and 40% were female and the median age was 73 (interquartile range 64−80) and 75 years (interquartile range 67−82 years), respectively.

Eligibility for SGLT2i Based on HFrEF Trial Criteria

Eligibility According to DAPA-HF Selection Criteria. Table 1, Figs. 1 and 2 in the trial scenario, 35% of outpatients with an EF of less than 40% were eligible for treatment with dapagliflozin. The major inclusion criteria limiting eligibility an HF duration of at least 2 months (71% eligible after applying this criterion) and the NT-proBNP criterion (83% eligible). The most common exclusion criterion (in 9% of cases) was a diagnosis of myocardial infarction or stroke within 12 weeks before registration. Notably, a systolic blood pressure of less than 95 mm Hg (5% of cases) and an eGFR of less than 30 mL/min/1.73 m^2 (6% of cases) were infrequent causes of exclusion. In the pragmatic and label scenarios 61% and 80% of patients, respectively, were eligible for treatment with dapagliflozin.

Eligibility Based on HFpEF Trial Criteria

*Eligibility According to EMPEROR-Reduced Selection Criteria (*Table 1, Figs. 1-2*).* In the trial scenario, 31% of patients with an EF of less than 40% were eligible for treatment with empagliflozin. The major inclusion criterion limiting eligibility was a history of HF 3 or more months before registration (only 65% eligible). The most common exclusion criteria were history of myocardial infarction, coronary revascularization and stroke within 3 months before registration (9%) and hypotension (8%). Severe kidney disease had a limited impact on eligibility (2% of the cases had an eGFR of <20 mL/min/1.73 m^2). Overall, in the pragmatic and label scenarios 55% and 81% of patients with an EF of less than 40%, respectively, were eligible for treatment with empagliflozin.

Eligibility According to DELIVER Selection Criteria. In the trial scenario, 30% of patients with an of EF 40% or greater were eligible for treatment

Table 1. Eligibility Based on Inclusion and Exclusion Criteria of DAPA-HF and EMPEROR-Reduced Trials

	DAPA-HF	EMPEROR-Reduced
No. of patients (denominator)	26,887	26,887
Inclusion criteria		
Written informed consent must be obtained before assessment is performed*	Assumed 100%	Assumed 100%
Age ≥18 years*	100%	100%
EF <40%*	100%	100%
NYHA functional class II−IV*	89.9%	89.9%
DAPA-HF: HF duration ≥2 months	70.7%	64.7%
EMPEROR-Reduced: HF duration ≥3 months		
NT-proBNP criterion*	83.1%	73.7%
DAPA-HF: Stable HF medications over the last 4 weeks*	Assumed 100%	Assumed 100%
EMPEROR-Reduced: Appropriate dose of medical therapy for HF consistent with prevailing local and international CV guidelines, stable for at least 1 week prior to Visit 1*		
Eligible − trial scenario: only inclusion criteria	*54.1%*	*44.3%*
Eligible - pragmatic scenario: only inclusion criteria (HF duration criterion considered as 100% eligible)	*76.2%*	*68.0%*
Exclusion criteria		
Receiving treatment with SGLT2i	Assumed 100%	Assumed 100%
EMPEROR-Reduced: Known allergy or hypersensitivity to any SGLT2i	-	Assumed 100%
Diabetes mellitus type 1*	92.5%	-
DAPA-HF: eGFR <30 mL/min/1.73m^2*	93.7%	98.4%
EMPEROR-Reduced: eGFR <20 mL/min/1.73m^2*		
DAPA-HF: SBP <95 mm Hg*	94.8%	91.6%
EMPEROR-Reduced: SBP <100 mm Hg*		
SBP ≥180 mm Hg	-	98.8%
EMPEROR-Reduced: Chronic pulmonary disease requiring home oxygen, oral corticosteroid therapy or hospitalization for exacerbation within 12 months; significant chronic pulmonary disease	-	Assumed 100%
EMPEROR-Reduced: Primary pulmonary artery hypertension	-	99.6%
DAPA-HF: previous HF hospitalization within 4 weeks	94.3%	99.4%
EMPEROR-Reduced: previous HF hospitalization ≤1 week		
DAPA-HF: MI, unstable angina, stroke or TIA within 12 weeks prior to enrolment	91.2%	-
DAPA-HF: PCI or CABG or valvular repair/replacement within 12 weeks prior to enrolment	94.2%	-
	-	91.3%

(*continued*)

Table 1 (*Continued*)

	DAPA-HF	EMPEROR-Reduced
EMPEROR-Reduced: MI, CABG, cardiovascular surgery, stroke, TIA within 3 months before enrolment		
DAPA-HF: Planned coronary revascularization, ablation of atrial flutter/fibrillation and valve repair/replacement.	Assumed 100%	-
EMPEROR-Reduced: Any severe valvular heart disease expected to lead to surgery during the trial period	-	Assumed 100%
DAPA-HF: Implantation of a cardiac CRT within 12 weeks	98.8%	97.7%
EMPEROR-Reduced: Implantation of ICD/CRT within 12 weeks		
EMPEROR-Reduced: Atrial fibrillation and heart rate >110/min	-	98.7%
EMPEROR-Reduced: Untreated ventricular arrhythmia with syncope in a patient without an ICD within 3 months prior to screening	-	Assumed 100%
DAPA-HF: Previous HTx or LVAD or expected implantation	Assumed 100%	Assumed 100%
EMPEROR-Reduced: HTx recipient, or listed for HTx. Currently implanted LVAD		
DAPA-HF: HF owing to restrictive cardiomyopathy, myocarditis, constrictive pericarditis, hypertrophic cardiomyopathy	98.7%	99.5%
EMPEROR-Reduced: Amyloidosis, HCM, pericardial constriction		
EMPEROR-Reduced: Diagnosis of peripartum cardiomyopathy or cardiomyopathy induced by chemotherapy within 12 months	-	Assumed 100%
Symptomatic bradycardia or second or third degree heart block without a pacemaker	Assumed 100%	Assumed 100%
DAPA-HF: Any condition outside the CV and renal disease area with a life expectancy of less than 2 years	Assumed 100%	Assumed 100%
EMPEROR-Reduced: Presence of any other disease than heart failure with a life expectancy of <1 year		
Active malignancy†	97.1%	94.5%
Hepatic impairment	98.5%	98.5%
EMPEROR-Reduced: Hemoglobin <9 g/dL	-	99.8%
EMPEROR-Reduced: Major surgery performed within 90 days prior to screening, or major scheduled elective surgery within 90 days after screening	-	Assumed 100%
EMPEROR-Reduced: Gastrointestinal disorders (Crohn, pancreatitis and liver disease within 1 year, and gastric and duodenal ulcers within 3 months)	-	97.9%
DAPA-HF: Known blood born disease	Assumed 100%	-
DAPA-HF: Women of child-bearing potential who are not willing to use contraception OR women who have a positive pregnancy test OR women who are breast feeding	Assumed 100%	Assumed 100%
EMPEROR-Reduced: Women who are pregnant or are nursing or who plan to become pregnant while in the trial		
DAPA-HF: Involvement in the trial design and conduct	Assumed 100%	
DAPA-HF: Previous randomization in the present study	Assumed 100%	–
DAPA-HF Participation in another clinical study with an IP during the last month prior to enrolment	Assumed 100%	–
DAPA-HF: Inability of the patient, in the opinion of the investigator, to understand and/or comply with study medications, procedures and/or follow-up, or any conditions that, in the opinion of the investigator, may render the patient unable to complete the study	Assumed 100%	–
EMPEROR-Reduced: Discontinuation of a SGLT2i for the purposes of study enrolment is not permitted	-	Assumed 100%
EMPEROR-Reduced: History of ketoacidosis	-	99.9%
EMPEROR-Reduced: Patients who must or wish to continue the intake of restricted medications or any drug considered likely to interfere with the safe conduct of the trial	-	Assumed 100%
EMPEROR-Reduced: Currently enrolled in another investigational device or drug study or are less than 30 days since the completion of a trial of another investigational device or drug study. Any patient receiving any investigational treatment other than the study medications for this trial	-	Assumed 100%
EMPEROR-Reduced: Chronic alcohol or drug abuse or any condition that, in the investigator's opinion, will make the patient unlikely to fulfil the trial requirements or complete the trial	-	Assumed 100%
EMPEROR-Reduced: Any other clinical condition that would jeopardize patient safety while participating in this trial or may prevent the subject from adhering to the trial protocol	-	Assumed 100%
Eligible - trial scenario: only exclusion criteria	*65.6%*	*71.5%*
Eligible - pragmatic scenario: only exclusion criteria (hypotension, and type 1 diabetes eGFR as only exclusion criteria)	*82.9%*	*83.6%*
Eligible (trial scenario)	**34.6%**	**31.3%**
Eligible (pragmatic scenario: HF duration criterion assumed 100% eligible; hypotension, eGFR and type 1 diabetes as only exclusion criteria)	**61.3%**	**55.0%**
Eligible label	**79.6%**	**81.1%**

CABG, coronary artery bypass grafting; CRT, cardiac synchronization therapy; CV, cardiovascular; DAPA-HF, Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; EMPEROR-Reduced, Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction; EF, ejection fraction; eGFR, estimated glomerular infiltration rate; HCM, hypertrophic cardiomyopathy; HF, heart failure; HTx, heart transplantation; ICD: implantable cardioverter defibrillator; LVAD, left ventricular assist device; MI, myocardial infarction; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; SGLT2i, Sodium Glucose co-transporter 2; TIA, transient ischemic attack.

*Criteria used in the pragmatic scenario.

†Defined as in Supplemental Table 1 for DAPA-HF and Supplemental Table 3 for EMPEROR-Reduced.

Table 2. Eligibility Based on Inclusion/Exclusion Criteria of DELIVER and EMPEROR-Preserved Trials

	DELIVER	EMPEROR-Preserved
No. of patients (denominator)	22,430	22,430
Inclusion criteria		
Written informed consent must be obtained before assessment is performed*	Assumed 100%	Assumed 100%
Age criterion* DELIVER: Age ≥40 EMPEROR-Preserved: Age ≥18	98.4%	100%
EF <40% *	100%	100%
NYHA function class II−IV*	83.3%	83.3%
DELIVER: HF duration ≥6 weeks EMPEROR-Preserved: HF duration ≥3 months	70.3%	62.8%
DELIVER: diuretic treatment	68.9%	-
NT-proBNP criterion*	81.2%	77.8%
DELIVER: Patients currently hospitalized for HF, must be off intravenous HF medications for at least 24 before randomization* EMPEROR-Preserved: Stable dose of oral diuretics for 1 week prior to randomization, if prescribed*	Assumed 100% (only outpatients included)	Assumed 100%
Eligible − trial scenario: only inclusion criteria	*41.7%*	*43.1%*
Eligible - pragmatic scenario: only inclusion criteria (HF duration criterion considered as 100% eligible; ongoing diuretic treatment for DELIVER excluded, all ages eligible)	*70.9%*	*68.1%*
Exclusion criteria		
Receiving treatment with SGLT2i	Assumed 100%	Assumed 100%
EMPEROR-Preserved: Known allergy or hypersensitivity to any SGLT2 inhibitors	-	Assumed 100%
DELIVER: Diabetes mellitus type 1*	92.8%	-
DELIVER: BMI >50 kg/m^2	99.7%	-
DELIVER: eGFR <25 mL/min/1.73 m^2* EMPEROR-Preserved: eGFR <20 mL/min/1.73 m^2*	96.6%	98.5%
DELIVER: SBP <95 mm Hg* EMPEROR-Preserved: SBP <100 mm Hg*	97.5%	95.9%
SBP ≥180 mm Hg	98.1%	98.2%
DELIVER: Chronic pulmonary embolism, severe pulmonary disease including COPD (i.e., requiring home oxygen, chronic nebulizer therapy or chronic oral steroid therapy, or hospitalization for exacerbation of COPD requiring ventilatory assist within 12 months prior to enrolment). EMPEROR-Preserved: Chronic pulmonary disease requiring home oxygen, oral corticosteroid therapy or hospitalization for exacerbation within 12 months; significant chronic pulmonary disease	Assumed 100%	Assumed 100%
Pulmonary artery hypertension	98.9%	98.9%
DELIVER: Probable alternative or concomitant diagnoses which could account for the patient's HF symptoms and signs.	Assumed 100%	-
EMPEROR-Preserved: previous HF hospitalization ≤1 week	-	99.5%
DELIVER: MI, unstable angina, stroke or TIA within 12 weeks prior to enrolment	93.7%	-
DELIVER: PCI or CABG or valvular repair/replacement within 12 weeks prior to enrolment	95.6%	
EMPEROR-Preserved: MI, CABG, cardiovascular surgery, stroke, TIA within 12 weeks prior to enrolment	-	93.5%
DELIVER: Planned coronary revascularization, ablation of atrial flutter/fibrillation and valve repair/replacement.	Assumed 100%	-
EMPEROR-Preserved: Any severe valvular heart disease expected to lead to surgery during the trial period	-	Assumed 100%
EMPEROR-Preserved: CRT (ever)	-	97.4%
EMPEROR-Preserved: Atrial fibrillation and heart rate >110/min	-	98.9%
EMPEROR-Preserved: Untreated ventricular arrhythmia with syncope in a patient without an ICD within 3 months prior to screening	-	Assumed 100%
EMPEROR-Preserved: ICD implant ≤3 months	-	99.7%
DELIVER: Previous HTx or LVAD or expected implantation EMPEROR-Preserved: HTx recipient, or listed for HTx currently implanted LVAD	Assumed 100%	Assumed 100%
Amyloidosis, HCM, pericardial constriction	98.6%	98.6%
DELIVER: Any condition outside the CV and renal disease area with a life expectancy of less than 2 years EMPEROR-Preserved: Presence of any other disease than HF with a life expectancy of <1 year	Assumed 100%	Assumed 100%
Active malignancy[†]	96.9%	94.1%
Hepatic impairment	98.7%	98.7%
EMPEROR-Preserved: Hemoglobin <9 g/dL	-	99.6%

(*continued*)

Table 2 (*Continued*)

	DELIVER	EMPEROR-Preserved
EMPEROR-Preserved: Major surgery performed within 90 days prior to screening, or major scheduled elective surgery within 90 days after screening	-	Assumed 100%
EMPEROR-Preserved: Gastrointestinal disorders (Crohn, pancreatitis and liver disease within 1 year, and gastric and duodenal ulcers within 3 months)	-	98.2%
DELIVER: Women of child-bearing potential who are not willing to use a method of contraception that is considered reliable in the judgment of the investigator OR women who have a positive pregnancy test at enrolment or randomization OR women who are breast feeding EMPEROR-Preserved: Women who are pregnant or are nursing or who plan to become pregnant while in the trial	Assumed 100%	Assumed 100%
DELIVER: Involvement in the planning and/or conduct of the study (applies to both AstraZeneca personnel and/or personnel at the study site)		-
DELIVER: Previous randomization in the present study		
DELIVER: Participation in another clinical study with an IP or device during the last month prior to enrolment		
EMPEROR-Preserved: Discontinuation of a SGLT2 inhibitor or combined inhibitor of SGLT1 and SGLT2 inhibitor for the purposes of study enrolment is not permitted	-	Assumed 100%
EMPEROR-Preserved: Known allergy or hypersensitivity to any SGLT2 inhibitors	-	Assumed 100%
EMPEROR-Preserved: History of ketoacidosis	-	99.9%
EMPEROR-Preserved: Patients who must or wish to continue the intake of restricted medications or any drug considered likely to interfere with the safe conduct of the trial	-	Assumed 100%
EMPEROR-Preserved: Currently enrolled in another investigational device or drug study or are less than 30 days since the completion of a trial of another investigational device or drug study. Any patient receiving any investigational treatment other than the study medications for this trial	-	Assumed 100%
EMPEROR-Preserved: Chronic alcohol or drug abuse or any condition that, in the investigator's opinion, will make the patient unlikely to fulfil the trial requirements or complete the trial	-	Assumed 100%
EMPEROR-Preserved: Any other clinical condition that would jeopardize patient safety while participating in this trial or may prevent the subject from adhering to the trial protocol	-	Assumed 100%
Eligible - trial scenario: only exclusion criteria	*74.4%*	*70.1%*
Eligible - pragmatic scenario: only exclusion criteria (hypotension, eGFR and type 1 diabetes criteria as only exclusion criteria)	*87.8%*	*87.9%*
Eligible (trial scenario)	**29.6%**	**31.6%**
Eligible (pragmatic scenario: HF duration criterion assumed 100% eligible; diuretic use criterion for DELIVER assumed 100% eligible, all ages considered eligible, hypotension and eGFR and type 1 diabetes as only exclusion criteria)	**60.8%**	**58.6%**
Label scenario	**73.8%**	**75.4%**

BMI, body mass index; COPD, chronic obstructive pulmonary disease; DELIVER, Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure; EMPEROR-Preserved, Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction. Other abbreviations as in Table 1.

*Criteria used in the pragmatic scenario.

†Defined as in Supplemental Table 2 for DELIVER and Supplemental Table 4 for EMPEROR-Preserved

with dapagliflozin. The main inclusion criteria limiting eligibility were again HF duration (≥6 weeks) (only 70% eligible) and ongoing diuretic treatment (as a surrogate for the trial criteria "at least intermittent need for diuretic treatment with recurrent dosing"; 69% eligible) (Table 2; Figs. 1 and 2). Impaired renal function (eGFR of <25 mL/min/1.73 m^2) excluded 3% of the patients. The main exclusion criteria were a history of myocardial infarction or stroke within 12 weeks before registration (6% of the cases). In the pragmatic and label scenarios 61% and 74% of patients with an EF of 40% or greater, respectively, were eligible for treatment with dapagliflozin.

Eligibility According to EMPEROR-Preserved Selection Criteria. In the trial scenario, 32% of patients with an of EF 40% or greater were eligible for empagliflozin. The major inclusion criteria limiting eligibility were again HF duration (≥3 months) (only 63% eligible) and the NT-proBNP criterion (78% eligible) (Table 2; Figs. 1 and 2). The main exclusion criteria were a history of myocardial infarction, coronary revascularization, and stroke within 12 weeks (6%), and active malignancy within 2 years before registration (6% of cases). Severe kidney disease (eGFR of <20 mL/min/1.73 m^2) excluded only 1% of the cases. Overall, in the pragmatic and label scenarios 59% and 75% of patients with an of EF 40% or greater, respectively, were eligible for treatment with empagliflozin. The impact of selected inclusion and exclusion criteria on eligibility rates in the trial and pragmatic scenarios is reported in Fig. 1.

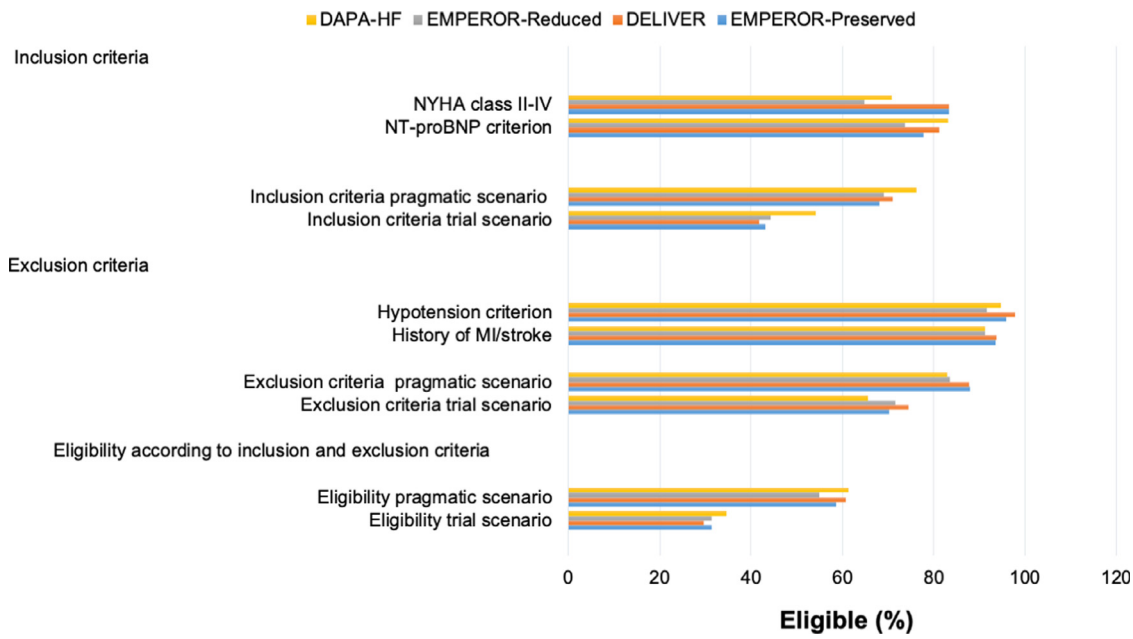

Fig. 1. Impact of selected inclusion and exclusion criteria on eligibility rates in the trial and pragmatic scenarios. DAPA-HF, Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; DELIVER, Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure; EMPEROR-Preserved, Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction; EMPEROR-Reduced, Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction; MI, myocardial infarction; NYHA, New York Heart Association.

Consistency Analysis

Eligibility rates in the consistency analyses, that is, missing values considered as eligible and complete case analysis, were overall consistent with the main analyses, i.e., on imputed data (Supplemental Tables 6 and 7).

Patient Characteristics and Outcomes in Eligible vs Non-eligible Patients in the Trial Scenario

The characteristics of patients according to their eligibility status in the trial scenario are reported in Supplemental Table 8 (DAPA-HF and EMPEROR-Reduced) and Supplemental Table 9 (DELIVER and

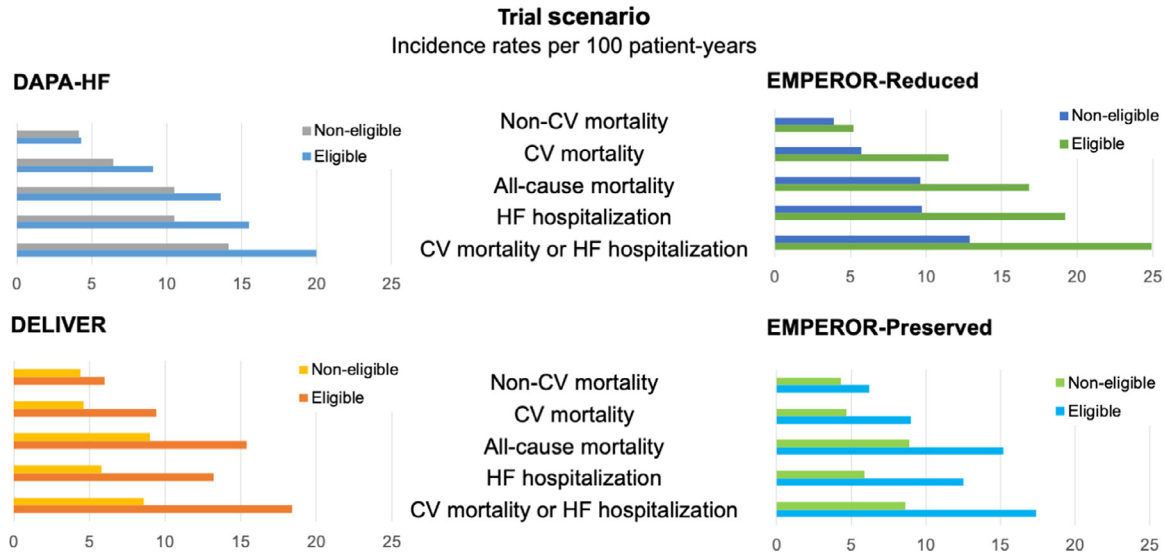

Fig. 2. Incidence rates in eligible vs non-eligible patients. CV, cardiovascular; DAPA-HF, Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; DELIVER, Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure; EMPEROR-Preserved, Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction; EMPEROR-Reduced, Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction; HF, heart failure.

EMPEROR-Preserved). Overall, eligible patients were older and had more severe HF (eg, a higher NYHA functional class, higher NT-proBNP levels, and a longer duration of HF) than non-eligible patients. Eligible patients were also more likely to have an eGFR of less than 60 mL/min/1.73 m^2, had greater cardiovascular comorbidity burden, and more often a history of chronic obstructive pulmonary disease. A history of myocardial infarction was generally more frequent in eligible patients, except for DELIVER, where an opposite finding was observed. Overall, eligible patients were more often treated with diuretics, and, using the entry criteria for the 2 HFrEF trials, eligible patients had a higher prevalence of HF device use (implantable cardioverter defibrillation or cardiac resynchronization therapy).

Event rates for all outcomes in eligible vs non-eligible patients are reported in Fig. 2 and Supplemental Table 10. The composite of cardiovascular mortality and HF hospitalization, HF hospitalization, and all-cause, cardiovascular, and noncardiovascular mortality event rates were higher in eligible vs non-eligible patients in all 3 scenarios, with a higher incidence rate ratio for cardiovascular vs noncardiovascular death.

Discussion

In this large, contemporary, non-selective real-world HF population, we found that eligibility for dapagliflozin and empagliflozin based on the eligibility criteria from the DAPA-HF, DELIVER, EMPEROR-Reduced, and EMPEROR-Preserved trials ranged between 30% and 35% when all the inclusion and exclusion criteria available in SwedeHF were applied. In the pragmatic scenario, where only the selection criteria most likely to influence the use of dapagliflozin and empagliflozin in clinical practice were considered, eligibility was higher and ranged between 55% and 61%, whereas it ranged between 74% and 81% in a label scenario. Eligibility according to each scenario was similar for both dapagliflozin and empagliflozin regardless of EF. Overall, in the trial scenario, eligible patients had more severe HF and more comorbidities, higher HF hospitalization rates, and higher cardiovascular and noncardiovascular mortality rates than non-eligible patients.

Eligibility rates according to the trial scenario for the 4 trials were similar despite some differences in selection criteria. Compared with DAPA-HF, EMPEROR-Reduced excluded more comorbidities (ie, a history of ketoacidosis, gastrointestinal disorders, and severe anemia), but these conditions were rare in SwedeHF and did not have a substantial impact on eligibility estimates. Similarly, EMPEROR-Preserved excluded more comorbidities compared with DELIVER.

An important inclusion criterion limiting eligibility according to the trial scenarios was the duration of HF at the time of the registration in SwedeHF (as a surrogate of HF duration at the time of enrolment in the trials). EMPEROR-Reduced required that patients were diagnosed with HF at least 3 months before the enrolment as compared with 2 months in DAPA-HF. EMPEROR-Preserved also required a diagnosis of HF 3 months before the enrollment, whereas more recently diagnosed HF was allowed in DELIVER ($\geq$6 weeks). For trial design purposes, HF duration is often used as a selection criterion to exclude new-onset HF, where clinical status often improves dramatically with the reversal of precipitating causes and treatment, and even though HF persists, it might be milder and associated with a lower risk of events. Setting a time from the first HF diagnosis also increases the likelihood of a correct HF diagnosis and that all diagnostic investigations are completed. Furthermore, a fixed time from HF diagnosis warrants the up-titration of guideline-recommended therapy at enrolment, and thus the efficacy and safety of the study drug is more likely to be tested on top of standard of care. Finally, this practice also avoids the potential confounding role of therapy optimization during the conduct of the trial, which might be differently performed in the study arms based on the different response to the study treatments and heterogeneous tolerance due to hypotension. On the other hand, a more recent HF diagnosis does not exclude the use of a treatment in the future, and patients with newly diagnosed HF should be repeatedly reevaluated for eligibility for new therapies. Therefore, because our study was cross-sectional, patients who did not fulfil the HF duration criterion of the trial scenarios at the date of registration in SwedeHF would likely do so later and thus become eligible at a different time point. Additionally, in both DAPA-HF and EMPEROR-Reduced, SGLT2i showed a benefit was evident after approximately 1 month.[21,22] These considerations support our use of a pragmatic scenario for eligibility assessment where HF duration was not included in the selection, yielding a higher proportion of patients who might be considered for SGLT2i treatment according to the trial selection criteria in a real-world setting.

Several of the exclusion criteria were time dependent, such as recent myocardial infarction, stroke or transient ischemic attack, cardiac surgery, and implantation of a cardiac device. Patients fulfilling these exclusion criteria in a trial scenario would be eligible after 3 months, which was the rationale for not considering these exclusion criteria in a pragmatic scenario. The implication of the use of time-dependent selection criteria, including recent cardiovascular events or interventions, is that SLGT2i

initiation should only be considered in clinically "stable" patients. However, SGLT2is have diuretic and hemodynamic effects that might be beneficial in the acute HF setting. Indeed, in the SOLOIST-WHF trial, sotagliflozin treatment initiated before or shortly after discharge from a HF hospitalization showed a decrease in cardiovascular deaths, HF hospitalizations, and urgent HF visits as compared with placebo.[=[13] Given such early benefits, there is evidence supporting a prompt initiation of all disease-modifying drugs in HFrEF.[23]

Following the results of the DAPA-HF trial, both the FDA and EMA approved dapagliflozin for symptomatic patients (NYHA functional class II−IV) with HFrEF. In our HFrEF population, 80% of patients were eligible for dapagliflozin according to the FDA/EMA label. Hypothesizing the same label for empagliflozin in HF and dapagliflozin in HFmrEF and HFpEF, we observed similar eligibility proportions for empagliflozin in HFrEF, that is, 81%, and slightly lower rates in HFmrEF and HFpEF, that is, 74% for dapagliflozin and 75% for empagliflozin. Overall, similar eligibility for dapagliflozin was observed in an analysis of the American Get with the Guidelines-Heart Failure (GWTG-HF) Registry, where according to the FDA HF labelling was 81% in patients hospitalized for HF.[24] Overall, these findings imply that applying regulatory agency-mandated criteria instead of stringent trial criteria significantly increases the number of patients with HF who become candidates for dapagliflozin and empagliflozin; therefore, a large proportion of patients not tested in the trials is instead eligible for treatments in real-world clinical practice. The high eligibility retrieved in the label scenario calls for an appropriate implementation of SGLT2i in clinical practice through effective communication to clinicians, educational activities, and the inclusion of structured treatment pathways in practical guidelines, even more so considering that guideline-directed use of HF treatments is in some cases scarce.[25]

Patient Characteristics and Outcomes

RCTs are usually considered to include younger, healthier patients, with fewer comorbidities compared with real-world patients with HF.[26] However, all 4 SGLT2i trials explored in our study used inclusion criteria to select more severe HF, which led eligible vs non-eligible patients in our analyses in the trial scenarios to have higher NT-proBNP levels, have a longer duration of HF, and be more likely in NYHA functional classes III−IV vs II, which in turn was associated with worse renal function, older age, more cardiovascular as well as noncardiovascular comorbidities, and consequently also with a higher risk of cardiovascular and noncardiovascular mortality. This outcome might seem rather surprising because HF trials try to enrich for cardiovascular vs noncardiovascular events because the primary outcome is cardiovascular and might suggest that the trial criteria were not excessively selective. By including patients with more severe HF, they probably also enrolled high proportions of noncardiovascular comorbidities. Consistently, although the risk of mortality and morbidity was significantly higher in eligible vs non-eligible patients for all the trials, eligibility was associated with a much higher risk of cardiovascular compared with noncardiovascular mortality.

The EMPEROR-Reduced trial selected patients with higher NT-proBNP levels. Consequently, eligible vs non-eligible patients according to the EMPEROR-Reduced criteria had a higher risk of cardiovascular death and HF hospitalization compared with eligible vs non-eligible patients according to DAPA-HF criteria, which is consistent with the higher event rates in the first vs the latter.

Notably, the event rates in eligible patients in our HFrEF analyses were substantially higher than that reported in the placebo arms of DAPA-HF and EMPEROR-Reduced.[9,10] Our real-world population differs from the trial populations in several important characteristics. Patients with HFrEF in SwedeHF compared with those in the trials were on average around 10 years older and had higher NT-proBNP levels, worse renal function, and more severe HF symptoms. Likewise, the event rate for the primary composite primary endpoint and for HF hospitalization in our patients with HFmrEF and HFpEF was higher than those occurring in the placebo arm of the EMPEROR-Preserved trial.[11] Eligible patients with HFpEF in SwedeHF were older and had a higher NYHA functional class and NT-proBNP levels compared with EMPEROR-Preserved trial population.

Thus, even though not necessarily limited by selection criteria, RCTs in HF still seem to include younger and healthier patients compared with the average real-world patient with HF.

Limitations

First, our study had a cross-sectional design; however, eligibility might change over time, reflecting the natural course of HF. Second, a major factor limiting eligibility was the short duration of HF. However, SwedeHF has very limited coverage in primary care where the first diagnosis of HF is likely made, and our HF duration is based on information from hospitals. Hence, an underestimation of the real HF duration in our study has to be taken into account. Finally, some data required for defining specific inclusion and exclusion criteria were not available in

SwedeHF or the NPR; therefore, we used slightly different definitions or surrogates.

For a few of the variables used to define eligibility (mainly body mass index, NT-proBNP, and NYHA functional class), there was a large proportion of missing data. We used imputation, taking into consideration the extensive number of measured variables available, to try to rectify any possible bias caused by the information missing at random. However, we could not rule out that data were also missing not at random, thereby possibly biasing the results. We, therefore, performed 2 sensitivity analyses (complete case analysis and missing as eligible) to further examine the effect of the missing data and examine the robustness of the results.

Conclusions

In a real-world outpatient HF setting, eligibility for dapagliflozin and empagliflozin based DAPA-HF, DELIVER, EMPEROR-Reduced, and EMPEROR-Preserved selection criteria ranged from 55% to 61% in a pragmatic scenario and from 74% to 81% in a label scenario, whereas about one-third of our HF population was eligible if all the trials' inclusion and exclusion criteria were applied strictly. Despite differences in selection criteria across the 4 trials, eligibility estimates were similar. Overall, eligible vs noneligible patients were older, had more severe HF, more cardiovascular comorbidities, and greater cardiovascular vs noncardiovascular event rates. Our data might help multiple stakeholders to improve trial design in HF by estimating the consequences of adopting specific inclusion criteria in terms of event rates, characteristics of the population enrolled, the feasibility of enrolment, and generalizability. Further, they may provide information for payers and health care authorities to estimate potential use of SGLT2i and ensuing costs.

Disclosures

TT discloses no conflict of interest related to this work and has received speakers fee from Novartis, Bayer, and Orion Pharma. GF discloses no conflicts of interest related to this work and has received speaker's fees from the European Society of Cardiology and research grant from Erling-Persson foundation outside the submitted work. LM discloses o conflicts of interest related to this work, and reports personal fees from Novo Nordisk, Sanofi Aventis, Astra Zeneca, MSD, Boehringer Ingelheim, and Amgen outside the submitted work. LB discloses no conflict of interest related to this work. FC reports no conflicts of interest related to this work and has received grants from the Swedish Research Council, Swedish Heart & Lung Foundation, and the European Foundation for the Study of Diabetes, as well as personal fees from Abbott, AstraZeneca, Bayer, Bristol-Myers Squibb, Merck Sharp & Dohme, Novo Nordisk, and Pfizer.

JM reports payments to my employer, Glasgow University, for my work on clinical trials, consulting and other activities from Alnylam, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Cardurion, Cytokinetics, Dal-Cor, GSK, Ionis, KBP Biosciences, Novartis, Pfizer, and Theracos; personal lecture fees from Abbott, Alkem Metabolics, Eris Lifesciences, Hikma, Lupin, Sun Pharmaceuticals, Medscape/Heart.Org, ProAdWise Communications, Radcliffe Cardiology, Servier, and the Corpus; and is the director of Global Clinical Trial Partners Ltd (GCTP). UD reports no conflict of interest related to this work. Outside the work submitted there are the following potential conflicts of interest: research grants to the author's institution from AstraZeneca, Pfizer, Boehringer Ingelheim, Boston Scientific, Roche Diagnostics and Vifor Pharma, and consultancies/honoraria from AstraZeneca, Novartis, Pfizer, and Amgen.

Dr Lund's institution received financial support from Boehringer Ingelheim to perform the current study. No conflict of interest related to this work. Outside the work submitted, there are the following potential conflicts of interest: research grants to author's institution and speaker's and/or consulting fees from Merck, AstraZeneca, Novartis, Bayer, Vifor-Fresenius, Boston Scientific, Pharmacosmos, Abbott, Myokardia, Sanofi, Lexicon, Boerhinger Ingelheim, Medscape, and Radcliffe cardiology. GS reports grants and personal fees from Vifor, grants and nonfinancial support from Boehringer Ingelheim, personal fees from Società Prodotti Antibiotici, other grants and personal fees from AstraZeneca, personal fees from Roche, personal fees from Servier, grants from Novartis, personal fees from GENESIS, personal fees from Cytokinetics, personal fees from Medtronic, and grants from Boston Scientific, outside the submitted work.

Authors' contributions

TT: data analysis, data interpretation, manuscript drafting.

GF: data analysis, data interpretation, manuscript drafting.

LM: data interpretation and critical revision for important intellectual content.

LB: data management, data analysis, data interpretation and critical revision for important intellectual content.

FC: data interpretation and critical revision for important intellectual content.

JM: conception, data acquisition, data interpretation and critical revision for important intellectual content.

UD: data acquisition, data interpretation and critical revision for important intellectual content.

LHL: conception and design, data interpretation, critical revision for important intellectual content.

GS: conception and design, data interpretation, critical revision for important intellectual content.

All authors approve the final version of the manuscript.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2022.04.011.

References

1. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–28.
2. 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.
3. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019;380:347–57.
4. Radholm K, Figtree G, Perkovic V, Solomon SD, Mahaffey KW, de Zeeuw D, et al. Canagliflozin and heart failure in type 2 diabetes mellitus: results from the CANVAS Program. Circulation 2018;138:458–68.
5. Fitchett D, Zinman B, Wanner C, Lachin JM, Hantel S, Salsali A, et al. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME(R) trial. Eur Heart J 2016;37:1526–34.
6. Kato ET, Silverman MG, Mosenzon O, Zelniker TA, Cahn A, Furtado RHM, et al. Effect of dapagliflozin on heart failure and mortality in type 2 diabetes mellitus. Circulation 2019;139:2528–36.
7. Cannon CP, Pratley R, Dagogo-Jack S, Mancuso J, Huyck S, Masiukiewicz U, et al. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. N Engl J Med 2020;383:1425–35.
8. Cosentino F, Cannon CP, Cherney DZI, Masiukiewicz U, Pratley R, Dagogo-Jack S, et al. Efficacy of ertugliflozin on heart failure-related events in patients with type 2 diabetes mellitus and established atherosclerotic cardiovascular disease: results of the VERTIS CV Trial. Circulation 2020;142:2205–15.
9. McMurray JJV, Solomon SD, Inzucchi SE, Kober L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019;381:1995–2008.
10. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med 2020;383:1413–24.
11. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Bohm M, et al. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med 2021;385:1451–61.
12. Solomon SD, de Boer RA, DeMets D, Hernandez AF, Inzucchi SE, Kosiborod MN, et al. Dapagliflozin in heart failure with preserved and mildly reduced ejection fraction: rationale and design of the DELIVER Trial. Eur J Heart Fail 2021;23:1217–25.
13. Bhatt DL, Szarek M, Steg PG, Cannon CP, Leiter LA, McGuire DK, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. N Engl J Med 2020;384:117–28.
14. Voors AA, Angermann CE, Teerlink JR, Collins SP, Kosiborod M, Biegus J, et al. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial. Nat Med 2022;28:568–74.
15. Savarese G, Vasko P, Jonsson A, Edner M, Dahlstrom U, Lund LH. The Swedish Heart Failure Registry: a living, ongoing quality assurance and research in heart failure. Ups J Med Sci 2019;235:65–9.
16. Koh AS, Tay WT, Teng THK, Vedin O, Benson L, Dahlstrom U, et al. A comprehensive population-based characterization of heart failure with mid-range ejection fraction. Eur J Heart Fail 2017;19:1624–34.
17. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC Public Health 2011;11:450.
18. Anker SD, Butler J, Filippatos GS, Jamal W, Salsali A, Schnee J, et al. Evaluation of the effects of sodium-glucose co-transporter 2 inhibition with empagliflozin on morbidity and mortality in patients with chronic heart failure and a preserved ejection fraction: rationale for and design of the EMPEROR-Preserved Trial. Eur J Heart Fail 2019;21:1279–87.
19. Packer M, Butler J, Filippatos GS, Jamal W, Salsali A, Schnee J, et al. Evaluation of the effect of sodium-glucose co-transporter 2 inhibition with empagliflozin on morbidity and mortality of patients with chronic heart failure and a reduced ejection fraction: rationale for and design of the EMPEROR-Reduced trial. Eur J Heart Fail 2019;21:1270–8.
20. McMurray JJV, DeMets DL, Inzucchi SE, Kober L, Kosiborod MN, Langkilde AM, et al. A trial to evaluate the effect of the sodium-glucose co-transporter 2 inhibitor dapagliflozin on morbidity and mortality in patients with heart failure and reduced left ventricular ejection fraction (DAPA-HF). Eur J Heart Fail 2019;21:665–75.
21. Packer M, Anker SD, Butler J, Filippatos G, Ferreira JP, Pocock SJ, 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;143:326–36.
22. Berg DD, Jhund PS, Docherty KF, Murphy SA, Verma S, Inzucchi SE, et al. Time to clinical benefit of dapagliflozin and significance of prior heart failure hospitalization in patients with heart failure with reduced ejection fraction. JAMA Cardiol 2021;6:499–507.
23. McMurray JJV, Packer M. How should we sequence the treatments for heart failure and a reduced ejection fraction? A redefinition of evidence-based medicine. Circulation 2021;143:875–7.
24. Vaduganathan M, Greene SJ, Zhang S, Grau-Sepulveda M, DeVore AD, Butler J, et al. Applicability of US Food and Drug Administration labeling for dapagliflozin to patients with heart failure with reduced ejection fraction in US clinical practice: The Get With the Guidelines-Heart Failure (GWTG-HF) Registry. JAMA Cardiol 2020;6:1–10.

25. Greene SJ, Butler J, Albert NM, DeVore AD, Sharma PP, Duffy CI, et al. Medical therapy for heart failure with reduced ejection fraction: the CHAMP-HF Registry. J Am Coll Cardiol 2018;72:351–66.

26. Van Spall HG, Toren A, Kiss A, Fowler RA. Eligibility criteria of randomized controlled trials published in high-impact general medical journals: a systematic sampling review. JAMA 2007;297:1233–40.