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CLINICAL RESEARCH

Comparison of Investigator-Reported and Centrally Adjudicated Heart Failure Outcomes in the EMPEROR-Reduced Trial

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ABSTRACT

BACKGROUND There is limited published information on outcome adjudication in heart failure (HF).

OBJECTIVES The authors sought to compare investigator reports (IRs) to a Clinical Events Committee (CEC) and the impact of SCTI (Standardized Clinical Trial Initiative) criteria.

METHODS In the EMPEROR-Reduced trial, the authors compared IRs to the CEC for concordance; treatment effect on primary composite outcome events; and the components first event hospitalization primarily for HF or cardiovascular mortality (CVM), prognosis after hospitalization for heart failure (HHF), total HHFs, and trial duration with and without SCTI criteria.

RESULTS The CEC confirmed 76.3% of IR events for the primary outcome (CVM: 89.1%; HHF: 73.7%). The HR for treatment effect did not differ between adjudication methods for the primary outcome (IR: 0.75 [95% CI: 0.66-0.85]; CEC: 0.75 [95% CI: 0.65-0.86]), its components, or total HHFs. The prognosis after first HHF for all-cause mortality and CVM also did not differ between IR or CEC. Interestingly, IR primary HHF with different CEC primary cause had the highest subsequent fatal event rate. Full SCTI criteria were present in 90% of CEC HHFs—with a similar treatment effect to non-SCTI. The IR primary event reached the protocol target number (841) 3 months earlier than CEC (4 months with full SCTI criteria).

CONCLUSIONS Investigator adjudication is an alternative to a CEC with similar accuracy and faster event accumulation. The use of granular (SCTI) criteria did not improve trial performance. Finally, our data suggest that consideration be given to broadening the HHF definition to include "for or with" worsening disease. (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction [EMPEROR-Reduced]; NCT03057977) (J Am Coll Cardiol HF 2023;11:407–417) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

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ABBREVIATIONS AND ACRONYMS

ACM = all-cause mortality

CEC = Clinical Events Committee

CRO = clinical research organization

CV = cardiovascular

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

HHF = hospitalization for heart failure

Patients with heart failure (HF) experience shortened survival and significant morbidity. Mortality is dominated by cardiovascular (CV) causes, principally pump failure and sudden death events. However, although morbidity in HF can take many forms, such as significant symptoms on activity and also at rest, it is often characterized by discrete events such as a hospitalization primarily for HF. In HF clinical trials, hospitalization for heart failure (HHF), as a morbidity, has come to have particular importance as part of a composite primary endpoint with CV death.[1-3] Such cause-specific composites have previously been analyzed as time to first event. More recently, however, this composite has come to include total HHFs as a larger expression of the patient experience and a key secondary endpoint in EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction).

The standard for adjudicating these specific outcomes in HF clinical trials has been the use of a Clinical Events Committee (CEC), and, more recently, there have been recommendations to use standard definitions including the use of defined specific criteria.[4-6] However, publications of recent HF clinical trials have raised questions about the benefits of central adjudication by the CEC compared to investigator-reported outcomes.[7,8] Central adjudication involves an experienced group of HF cardiologists who apply a consistent set of criteria, whereas site investigators use direct knowledge of the patient and, usually, the clinical event. Drawbacks of the former approach include a lack of availability of specific details if objective criteria are required, while the investigator-reported approach may involve inconsistent definitions that might be accentuated in worldwide trials with sites in different geographic regions. Regardless of the method of endpoint assessment, HF clinical trials have usually considered that an HHF endpoint requires HF to be the primary reason for admission.

The EMPEROR-Reduced trial was a worldwide study to evaluate the effects of sodium-glucose transport protein 2 (SGLT2) inhibition with empagliflozin in patients with heart failure with reduced ejection fraction (HFrEF).[9] The trial demonstrated a significant reduction with empagliflozin in the primary composite outcome of CV death and HHF as well as for total HHFs with empagliflozin. The purpose of this analysis is to examine adjudication in this study: principally, to compare CEC and investigator assessments for concordance, impact on the primary outcome, and prognosis after nonfatal HHF.

METHODS

The data, analytic methods, and study materials will be made available to other researchers for purposes of reproducing the results or replicating the procedure.

The EMPEROR-Reduced trial was a randomized, double-blind, parallel-group, placebo-controlled, event-driven study of 3,730 patients who had chronic HF (functional class II, III, or IV) with a left ventricular ejection fraction of ≤40% who were randomly assigned to receive either empagliflozin or placebo in addition to recommended HF therapies. The study design has previously been described in detail.[10] Ethics approval was obtained at each study site, and informed consent was obtained from all study participants. The primary endpoint was the time-to-first-event analysis of the combined risk of CEC-adjudicated CV death or HHF. In the statistical plan, the first key secondary endpoint was the occurrence of adjudicated HHF (first and recurrent).

HF EVENTS. Full definitions of the clinical events from the CEC charter are included in the Supplemental Methods. Per the CEC charter, HHF events were those in which HF was the primary reason for admission of at least 12 hours' duration. This definition required criteria from the previously published SCTI (Standardized Clinical Trial Initiative): objective evidence of new or worsening HF (2 physical examination findings or 1 physical examination finding and 1 laboratory finding), and treatment for HF.[6] Treatments included intensification of

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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TABLE 1 Summary of Event Numbers by Type of Assessment

	Patients With Primary Event	Number of Patients With HHF/CV Death Contributing to Primary Event	Proportion of CV Deaths Contributing to Primary Endpoint	CV Deaths	Number of Patients With HHF	Total Number of HHFs	CEC-Confirmed Primary Events	CEC-Confirmed CV Deaths	CEC-Confirmed Number of HHFs
Investigator defined	951 (25.5)	746 (20.0)/205 (5.5)	21.6	403 (10.8)	746 (20.0)	1,231	726 (76.3)	359 (89.1)	907 (73.7)
Adjudicated	823 (22.1)	588 (15.8)/235 (6.3)	28.6	389 (10.4)	588 (15.8)	941			
Adjudicated excluding non-SCTI HHF	778 (20.9)	538 (14.4)/240 (6.4)	30.8	389 (10.4)	538 (14.4)	848			
Non-SCTI HHF	45[a]				83	93			

Values are n (%). [a]Additional patients with primary event based on inclusion of non-SCTI HHF in primary endpoint definition.
CEC = Clinical Events Committee; CV = cardiovascular; HHF = hospitalization for heart failure; SCTI = Standardized Clinical Trial Initiative.

oral diuretics, or initiation of intravenous diuretic agents or vasoactive medications, or a mechanical or surgical intervention.

At the first CEC adjudication meeting (May 2018), the committee identified events that the committee members agreed were HHF but that did not meet the full SCTI criteria, largely because of lack of documentation of physical findings. These events were placed in a separate category, and after further such events were identified subsequent CEC adjudication meetings, the CEC proposed to the Steering Committee and study sponsor that the definition of HHF be modified so that such events would be included in it. The updated criteria allowed events in which patients had HF symptoms and received specific treatment to be included for HHF, with unanimous agreement by the CEC. The specifics of the revised definition were shared with the U.S. Food and Drug Administration (FDA) in September 2019.

INVESTIGATOR-REPORTED EVENTS. Site investigators were directed to report all deaths and all events that they considered were a primary HHF along with a narrative. They were also asked to fill out a checklist following the SCTI criteria that included symptoms, physical and laboratory findings, and treatments. However, investigator-reported HHF events in the database did not require the presence of specific criteria but only the investigator assessment of HHF.

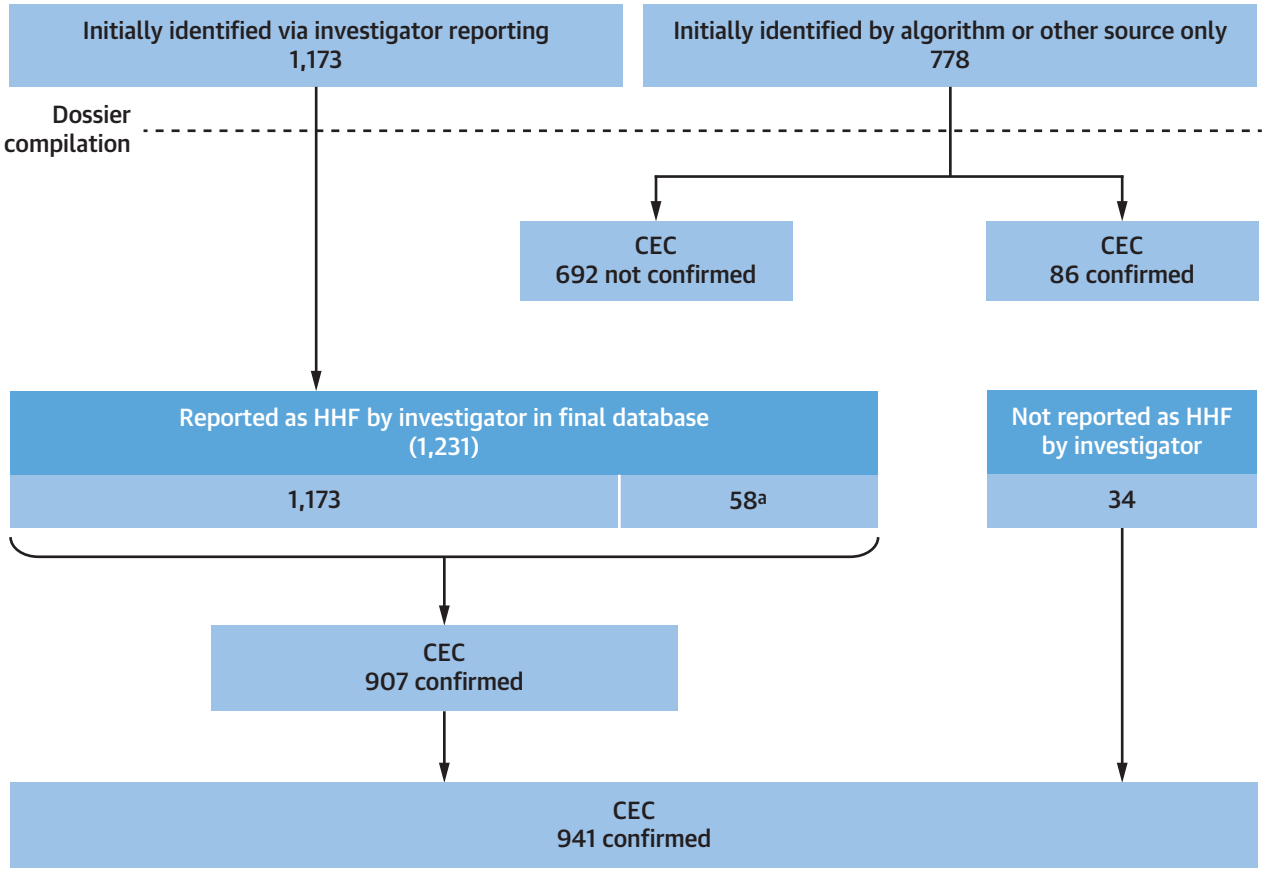
ADDITIONAL METHODS OF ENDPOINT COLLECTION. Because all hospitalizations or CV hospitalizations were not required to be adjudicated, additional methods were used to ensure that potential outcome events were not missed. These methods included site monitoring, medical manual review of Adverse Events by the clinical research organization (CRO) (IQVIA) and the sponsor, and the use of an algorithm-based process. This algorithm consisted of a programmatic review of safety databased on Medical Dictionary for Regulatory Activities (MedDRA) reported terms combined together with other safety data (eg, intravenous HF treatments and urgent visits) to identify events that met prespecified criteria, which "triggered" the requirement for event adjudication. CRO/sponsor-identified events are described as "other source" in this paper.

CENTRAL ADJUDICATION PROCESS. The EMPEROR-Reduced Cardiology CEC consisted of 8 cardiologists experienced in HF and endpoint adjudication. All CEC members reviewed and approved the CEC adjudication charter, which contained the process and definitions.

A dossier was compiled for each event that required adjudication and submitted to 2 adjudicators for review. All fatal events were further assessed by the full committee at teleconference or face-to-face sessions with presentation by the 2 initial reviewers. The CEC performed a final adjudication for fatal events at these meetings. The process for nonfatal events was particularly designed to capture all qualifying HHFs. To this end, the process mandated that a final adjudication would occur if the 2 adjudicators agreed with the initial assessment by the site investigator; otherwise, the event would be remanded to a full committee discussion for a final adjudication. A schematic of the adjudication process from the charter is included in Supplemental Methods and Supplemental Figures 1 and 2.

STATISTICAL ANALYSIS. For the purposes of this report, HHFs were analyzed as follows: investigator-reported events were compared to CEC-adjudicated events for concordance and subsequent fatal outcome analyses. Investigator-reported events for this comparison did not include events identified by the algorithm. CEC-adjudicated HHFs were analyzed both by including the non-SCTI HHFs and excluding these events, which were then analyzed separately. In this paper, events with full SCTI criteria are referred to as SCTI HHF, and events without full

CENTRAL ILLUSTRATION **Event Flowchart of Potential HHF Events: Relationship Between Initial Method of Identification, Final Investigator-Reported Status, and CEC Confirmation**



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[a]58 events initially identified via the algorithm were also reported by the investigator as HHF (6 out of those not confirmed by CEC and 52 events confirmed by CEC).
CEC = Clinical Events Committee; HHF = hospitalization for heart failure.

criteria are referred to as non-SCTI-HHF events. The differing categorization of events was compared to subsequent prognosis for subsequent CV death or HHF, CV death, and all-cause mortality (ACM). For calculation of fatal incidence rates, the time from onset of first event to CV death/ACM was considered. HRs were estimated relative to patients without adjudicated HHF and without investigator-reported HHF based on a Cox proportional hazards model including a time-dependent covariate for the type of first event, treatment, and treatment by time-dependent covariate interaction term as well as adjustment for baseline covariates of age, sex, geographic region, diabetes status, left ventricular ejection fraction, and estimated glomerular filtration rate. SAS version 9.4 was used for statistical analysis.[11]

RESULTS

There were 3,730 patients enrolled in the EMPEROR-Reduced study: 1,867 in the placebo arm and 1,863 in the empagliflozin treatment arm. The baseline characteristics of these patients have been previously presented. Baseline characteristics of the patients with HHF and those without are included in Supplemental Table 1. Although there were minor differences in many baseline characteristics, those with HHF were more likely to have had a previous HHF within the preceding 12 months, more likely to have diabetes mellitus, and a higher N-terminal pro-B-type natriuretic peptide level.

INVESTIGATOR-REPORTED VS CEC-ADJUDICATED EVENTS. There were 951 investigator-reported primary events—of which 726 were confirmed by the CEC

(76.3%). The CEC identified 823 primary outcome events with a slightly higher percentage of CV deaths (29% vs 22%). For the components of the primary outcome, investigators reported 403 CV deaths; 359 of these were confirmed by the CEC (89.1%), which overall adjudicated 389 CV deaths. For HHF, there were 1,231 investigator-reported HHF events in 746 patients, with the CEC confirming 907 (73.7%) (Table 1). The CEC adjudicated a total of 941 HHFs in 588 patients, which included 34 HHF events that were reported by the algorithm but not investigators. The investigator-reported total includes 58 hospitalizations initially reported by algorithm (Central Illustration).

The CEC-adjudicated events included 848 HHF events in 538 patients that satisfied the initial HHF definition (SCTI criteria), and there were 93 HHF events involving 83 patients without full SCTI criteria but meeting the revised definition (Table 2). These are discussed in a later section. There were 324 investigator-reported HHF events, involving 281 patients, for which the CEC did not confirm HF as the primary cause of admission, with an alternate diagnosis in 304. These events are categorized by the primary cause of admission in Table 3.

NON-INVESTIGATOR-IDENTIFIED EVENTS: ALGORITHM METHOD OR MEDICAL REVIEW. All deaths were reported by the sites. The majority of HHF events were also reported by the sites, although there were other events reported by the algorithm and CRO/sponsor as indicated in the Methods section. A compilation of investigator-reported, algorithm-generated, and CRO/sponsor events with their relation to the CEC adjudication process is seen in the Central Illustration. As detailed in Table 2, of 701 initially algorithm-identified potential HHFs, 83 (11.8%) were confirmed by the CEC. The CEC did not generate additional confirmed HHF events, and of 76 potential events identified by the CRO/sponsor, 3 (3.9%) were confirmed by the CEC.

RELATION OF THE ADJUDICATION METHOD TO THE PRIMARY ENDPOINT. In the assessment of treatment effect, for the 951 investigator-reported primary events (534 placebo; 417 empagliflozin) and 823 CEC-adjudicated primary outcome events (462 placebo; 361 empagliflozin), the HR for time to first investigator-reported primary outcome event (CV death or HHF) was nearly identical, as seen in Figure 1, and both adjudication methods demonstrated statistical significance in the treatment group. For the components of the primary outcome, there were again very similar HRs for treatment effect (Figure 1) with both adjudication methods.

TABLE 2 Concordance Between Adjudicated and Investigator-Reported Events as Initially Reported by Site

Event Initially Identified by	Adjudicated HHF (SCTI)	Adjudicated HHF (Non-SCTI)	No Event (Adjudicated)	Unable to Adjudicate Because of Insufficient Information	Total
Investigator	769 (65.6)	86 (7.3)	309 (26.3)	9 (0.8)	1,173 (100)
Algorithm	76 (10.8)	7 (1.0)	618 (88.2)	0	701 (100)
CEC	0	0	1 (100)	0	1 (100)
Other	3 (3.9)	0	73 (96.1)	0	76 (100)
Total	848 (43.5)	93 (4.8)	1,001 (51.3)	9 (0.5)	1,951 (100)

Values are n (%).
Abbreviations as in Table 1.

ENDPOINT DEFINITION: SCTI AND NON-SCTI HHFs. The CEC identified 93 HHF events that did not meet the original HHF definition (SCTI criteria) because 1 or more objective clinical findings of HF were missing. These events occurred in 83 patients, and 50 were a first HHF, resulting in 45 additional patients with a primary endpoint event (Table 1). The details of these patients and durations of their hospitalizations are shown in Supplemental Table 2 with comparison to the events meeting the criteria for an SCTI HHF. The inclusion or exclusion of non-SCTI events did not materially influence the treatment effect, as seen in Supplemental Table 3.

METHOD OF ADJUDICATION AND ENDPOINT ACCUMULATION. Investigator-reported primary outcome events reached the predetermined target number of 841 adjudicated primary events 3 months earlier than events confirmed by CEC adjudication (Supplemental Table 4). Considering CEC-adjudicated events, the addition of non-SCTI primary events decreased the duration of the trial by 1 month; hence, the use of SCTI events with full criteria would have produced a trial of 4 months' longer duration than investigator-reported events.

PROGNOSIS FOLLOWING HHF: INVESTIGATOR-REPORTED HHF VS CEC-ADJUDICATED HHF. The prognosis for fatal events (both all cause and CV) after or during a first HHF with investigator report or CEC confirmation is seen in Figure 2. Both methods of adjudication provide a similar subsequent prognosis for incidence rates and risk in comparison to subjects without an HHF during the study, particularly when SCTI criteria are used. It is notable that investigator-reported HHF not confirmed by the CEC had the worst subsequent fatal prognosis, with further details in the following section.

INVESTIGATOR-RELATED HHF NOT CONFIRMED BY THE CEC AS PRIMARY HHF. There were 324 investigator-reported HHF events, involving 281

TABLE 3 Adjudication Outcome of Investigator-Reported HHF Events That Were Not Confirmed by the CEC

	Total
Total number of investigator-reported HHF events not confirmed by the CEC	324 (100.0)
Myocardial infarction (including potential silent myocardial infarction)	4 (1.2)
Unstable angina	2 (0.6)
Chest pain	7 (2.2)
Complications of heart failure therapy	6 (1.9)
Atrial fibrillation/atrial flutter	23 (7.1)
Ventricular arrhythmia	12 (3.7)
Hypertension	2 (0.6)
Other cardiac cause	135 (41.7)
Noncardiac cause	113 (34.9)
Pulmonary	19 (5.9)
Anemia	1 (0.3)
Renal	3 (0.9)
Gastrointestinal	12 (3.7)
Pancreatic	1 (0.3)
Infection (includes sepsis)	41 (12.7)
Hemorrhage that is neither cardiovascular bleeding or a stroke	1 (0.3)
Trauma	4 (1.2)
Neurologic (noncardiovascular)	1 (0.3)
Malignancy	4 (1.2)
Other noncardiovascular causes	26 (8.0)
Unable to adjudicate because of insufficient information	20 (6.2)

Values are n (%).
Abbreviations as in Table 1.

patients, for which the CEC did not confirm HF as the primary cause of admission. These events are categorized by the primary cause of admission in Table 3, with 304 alternate primary diagnoses and 20 without sufficient information. As noted, the highest subsequent fatal event rate, compared to those without an HHF, was observed in this patient group (Figure 2), with an HR of 10.54 (95% CI: 7.94-13.98) for CV death and an HR of 11.60 (95% CI: 9.19-14.64) for ACM.

PROGNOSIS RELATING TO DOCUMENTATION FOR ADJUDICATED EVENTS: SCTI AND NON-SCTI. Consistent with the vigorous data accumulation noted in the Methods, more than 90% of patients with CEC-confirmed HHF contained adequate SCTI criteria (n = 538), and <10% did not. As seen in Figure 2, those without SCTI criteria had a more favorable subsequent prognosis for fatal events than those with SCTI criteria.

DISCUSSION

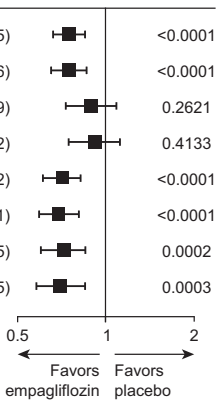
In this study of adjudication in the EMPEROR-Reduced HF trial, there was a high concordance between the CEC-adjudicated and investigator-reported events for CV death but a discordance in approximately one-quarter of HHF events. This resulted in substantial discordance between the investigator-reported and the CEC-adjudicated events on the primary outcome. However, the HR between empagliflozin and placebo for the primary composite outcome and its components did not differ between the 2 methods of endpoint assessment. Investigator-defined HHF events had a similar subsequent mortality risk to those confirmed by the CEC, and HHF events not considered a primary hospitalization cause by the CEC had a higher subsequent CV and ACM risk. Most HHFs had full SCTI documentation, but those without tended to have an attenuated subsequent risk of death. Investigator-defined primary event total reached the protocol-defined event number 3 months earlier than numbers confirmed by the CEC.

Given the importance of cause-specific events such as CV death and HHF in HF trials, it is important to consider how to optimally assess such events. HF patients commonly have several comorbidities, and these often make it difficult to provide a primary cause of a death or hospitalization. Although there is interest in defining endpoints, including a recent focus on specific criteria for HHF, there have been few publications on the actual adjudication process itself, which includes the important question of whether the adjudication should be done on the data provided by investigator report or by a central adjudication committee. A recent meta-analysis reviewed 39 studies in CV disease and concluded that blinded central adjudication and onsite assessment produced similar HRs, although only 1 HF study (CHARM [Candesartan in Heart Failure—Assessment of Reduction in Mortality and Morbidity]) was included in this analysis.[12] Two publications that did examine the adjudication process in HF—BEST (Bucindolol Estimation of Survival Trial)[13] and SHIFT (Systolic HF Treatment With IF Inhibitor Ivabradine Trial)[7] noted results similar to this paper. The current study adds to the published reports in that it involves a positive HF study in patients with reduced ejection fraction and assesses the subsequent prognosis of adjudicated nonfatal events, the impact on the duration of the study, and the use of an algorithm for additional potential outcome events.

CEC VS INVESTIGATOR ADJUDICATION. Although the CEC confirmed the majority of events comprising the primary outcome (76.3%), there was significant discordance that differed between the components of the composite endpoint, with higher confirmation rates of CV deaths than HHFs. Because HHF is invariably the major component of this composite

FIGURE 1 Efficacy Outcomes Based on Investigator vs CEC Assessment

Endpoint	Placebo (N=1867) n (%)	Placebo (N=1867) Incidence rate per 100 PY (95% CI)	Empagliflozin (N=1863) n (%)	Empagliflozin (N=1863) Incidence rate per 100 PY (95% CI)	HR (95% CI)	*p*-value
Time to first event of CV death or HHF, Investigator	534 (28.6)	25.00 (22.92, 27.16)	417 (22.4)	18.62 (16.88, 20.45)	0.75 (0.66, 0.85)	<0.0001
Time to first event of CV death or HHF, Adjudicated	462 (24.7)	21.00 (19.13, 22.96)	361 (19.4)	15.77 (14.19, 17.44)	0.75 (0.65, 0.86)	<0.0001
Time to CV death, Investigator	212 (11.4)	8.54 (7.43, 9.72)	191 (10.3)	7.71 (6.66, 8.85)	0.89 (0.73, 1.09)	0.2621
Time to CV death, Adjudicated	202 (10.8)	8.13 (7.05, 9.29)	187 (10.0)	7.55 (6.51, 8.67)	0.92 (0.75, 1.12)	0.4133
Time to first HHF, Investigator	429 (23.0)	20.08 (18.23, 22.03)	317 (17.0)	14.16 (12.64, 15.76)	0.71 (0.61, 0.82)	<0.0001
Time to first HHF, Adjudicated	342 (18.3)	15.55 (13.94, 17.24)	246 (13.2)	10.75 (9.45, 12.13)	0.69 (0.59, 0.81)	<0.0001
Total HHF, Investigator	710	–	521	–	0.72 (0.60, 0.85)	0.0002
Total HHF, Adjudicated	553	–	388	–	0.70 (0.58, 0.85)	0.0003



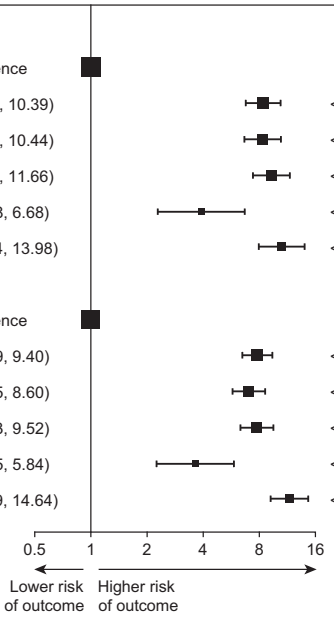
CV = cardiovascular; HHF = hospitalization for heart failure; PY = patient-years.

outcome, the discordance in HHF adjudication (for both HHF components of the primary outcome and total HHFs) becomes particularly important. There are likely 2 major reasons for the discordance: 1) the use of specific granular criteria (SCTI) by the CEC but not the investigators; and 2) disagreement on the primary reason for admission. For the former, the protocol mandated that CEC use specific granular evidence of symptoms, physical signs, laboratory values, and treatment for adjudicating HHF events. Even when the CEC determined that an event was an HHF but lacked full criteria, the following criteria had to be present: HHF as the primary reason for admission, specific therapy, and committee consensus. These events were 10% of the total CEC HHF adjudications. The investigators had no requirement for such criteria to be present, although they were asked to include them on a checklist and in a narrative. Although the use of specific criteria by the CEC certainly was responsible for some of the discordance with investigators, it may have not been the larger reason. In the recent report from the SHIFT study, the discordance between the CEC and investigators for HHF events was less than EMPEROR-Reduced (84%), although neither method of adjudication in SHIFT required the use of specific criteria.

A larger area of disagreement between the CEC and investigators may involve the primary reason for admission. As indicated in this paper, 26% of investigator-reported HHF events were assessed as having a different primary cause for admission by the CEC. The CEC-confirmed events were only those hospitalizations in which worsening HF was the primary reason for the hospitalization, which would not include an event where HF was present but another cause was the primary reason for admission, such as chronic obstructive pulmonary disease exacerbation, pneumonia, or atrial fibrillation, among others. An alternative approach would be to consider such events as indicating HHF even though there was another more important contributor—therefore, "for or with" worsening HF. This is not usually done in clinical trials, although this was the approach in the previous COPERNICUS (Carvedilol Prospective Randomized Cumulative Study), in which the adjudication of an endpoint for HF was met if the admission was "for or with" this diagnosis.[14] The primary reason for admission is often a subjective decision on an event, and this broader categorization—which still involves HF worsening—may explain the results in this study in which investigator HHF events had very similar treatment efficacy and similar subsequent mortality to CEC-adjudicated events. In those HHF events not confirmed by the CEC, the overall prognosis (ACM) would be in part influenced by the comorbidity noted by the CEC adjudication. However, the influence of worsening HF is likely the primary driver for the worse prognosis after these events, because the indicated relative risk for a CV death was 10.54 relative to those without an HHF (**Figure 2**).

FIGURE 2 Time to Subsequent Fatal Event After or During HHF Event

	Patients with event type N	Patients with subsequent event n (%)	Incidence rate per 100 PY (95% CI)[a]	HR (95% CI)[b]	*p*-value
Time to subsequent CV death					
No adjudicated and no investigator-reported HHF	2970	198 (6.7)	5.05 (4.37, 5.77)	Reference	–
Investigator-defined HHF	746	187 (25.1)	33.42 (28.80, 38.38)	8.39 (6.77, 10.39)	<0.0001
Adjudicated HHF	588	154 (26.2)	34.51 (29.27, 40.17)	8.33 (6.65, 10.44)	<0.0001
SCTI HHF	538	149 (27.7)	38.18 (32.30, 44.55)	9.28 (7.39, 11.66)	<0.0001
Non-SCTI HHF	83	15 (18.1)	19.69 (11.02, 30.83)	3.90 (2.28, 6.68)	<0.0001
Investigator HHF not confirmed by CEC	281	75 (26.7)	44.10 (34.68, 54.62)	10.54 (7.94, 13.98)	<0.0001
Time to subsequent all-cause mortality					
No adjudicated and no investigator-reported HHF	2970	265 (8.9)	6.75 (5.97, 7.59)	Reference	–
Investigator-defined HHF	746	245 (32.8)	43.79 (38.47, 49.44)	7.81 (6.49, 9.40)	<0.0001
Adjudicated HHF	588	184 (31.3)	41.23 (35.49, 47.40)	7.03 (5.75, 8.60)	<0.0001
SCTI HHF	538	176 (32.7)	45.10 (38.69, 52.01)	7.76 (6.33, 9.52)	<0.0001
Non-SCTI HHF	83	19 (22.9)	24.94 (15.01, 37.34)	3.63 (2.25, 5.84)	<0.0001
Investigator HHF not confirmed by CEC	281	117 (41.6)	68.79 (56.89, 81.80)	11.60 (9.19, 14.64)	<0.0001



CEC = Clinical Events Committee; SCTI = Standardized Clinical Trial Initiative; other abbreviations as in Figure 1.

The concept that HF could, perhaps to a varying degree, contribute to a hospitalization has recently been considered as a probabilistic approach to adjudication in PARAGON-HF (Prospective Comparison of ARNI With ARB Global Outcomes in HF With Preserved Ejection Fraction) study during a recent FDA Cardiorenal Panel hearing.[15,16]

The investigator-reported events may, then, have represented a broader metric of worsening HF than the CEC-adjudicated events, which focused on HF as the primary cause of admission—overwhelmingly with specific criteria. How valid are these investigator-reported events for assessing worsening disease? At least considering the prognosis after first HHF for fatal events, our analysis indicates that both CV death and ACM rates subsequent to a first HHF admission are similar between the methods of adjudication. There is no published analysis addressing this issue as this study does, but briefing documents for the recent FDA hearing on PARAGON-HF contain comparable data: an exposure-adjusted rate for ACM post-first HHF was similar for the 2 approaches to adjudication—CEC confirmed (18.6/100 patient-years; 95% CI: 16.1-21.3) and investigator reported (18.7/100 patient-years; 95% CI: 14.9-23.1).[15]

NON–INVESTIGATOR-REPORTED EVENTS AND ADJUDICATION. An editorial to the SHIFT study appropriately raised the caveat that CEC adjudication could include events that were identified by processes that did not involve the investigators.[17] In EMPEROR-Reduced, this principle involved the use of an algorithm, as indicated in the Methods. The CEC confirmed a significantly lower percentage of these algorithm events than the investigator-defined HHF events (11.8% vs 76.3%). The study processes did not require investigator reassessment of all of these events, and therefore, an agreement rate for investigators is not available but would likely add some events to an investigator-defined total.

SCTI HHFs AND NON-SCTI HHFs. Per protocol, the EMPEROR-Reduced CEC was initially required to use the specific SCTI criteria. Despite extensive efforts to obtain granular elements, the CEC realized very early that there were events considered to be HHFs with adequate hospitalization duration and specific HF treatment but that did not have documentation of the full SCTI criteria (usually missing physical signs). The results, as stated earlier, indicate that even with the elaborate processes in place, approximately 10% of HHFs without the full SCTI criteria met the amended

criteria for the HHF endpoint. The explanation for the attenuated subsequent risk of the patients whose HHFs did not have full documentation is not clear—whether this represents miscategorized events, less morbid events (characterized by fewer granular elements of HF), or a spurious result cannot be determined by the current data.

Could the difficulties with acquisition of the specific criteria of the SCTI guidelines have an important effect on clinical trial outcomes? There are no direct data that have been published, although the PARAGON-HF study experience before the FDA is relevant.[15,18] In the public record, the FDA Cardiorenal Panel presentation included results of a readjudication of 516 events not confirmed by the CEC, some of which were described as lacking documentation.[15] The resulting readjudication, which also included a probabilistic approach, described earlier, then led to a statistically favorable result.[19] More recently, PARADISE-MI (Prospective ARNI vs ACE Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events After MI) reported findings that investigator-reported events were associated with a favorable effect of sacubitril valsartan on the primary outcome, whereas a statistically significant effect was not seen with the CEC adjudication, which included fewer events.[20]

WHAT IS THE EFFECT OF THE METHOD OF ADJUDICATION AND ENDPOINT DEFINITION ON A PRIMARY OUTCOME? The ability to expand a primary outcome with additional events with the same effect size of the tested intervention could be expected to favorably affect the duration of the trial. Because many trials are endpoint driven, the time required to accumulate a prespecified number of events (eg, 841 in EMPEROR-Reduced) would be achieved sooner if investigator-reported events accumulated quickly, as was the experience in the current study, where the primary events accumulated 3 months earlier compared to the CEC adjudication. Because the CEC-adjudicated events included those with both SCTI and non-SCTI documentation, the gap would be approximately 4 months if just SCTI HHF events were used. The composition of the primary outcome did differ slightly in that it comprised a larger component of CV deaths for CEC events. The findings that investigator-reported events had a similar HR but enabled a more rapid accumulation of events, although not limited to a rigid set of HF findings, does not suggest a strong need for the use of criteria such as SCTI for HFrEF study.

STUDY LIMITATIONS. EMPEROR-Reduced was a worldwide clinical trial in HFrEF. Criteria for admission and care vary in different regions of the world, which, of course, can influence decisions to admit patients, and admissions often occur at hospitals unrelated to the investigator's site. As discussed, investigators did not receive specific guidance on reporting HHF but were asked to provide their clinical judgment. Whether the addition of the request for a narrative and a checklist influenced the investigators' assessments of a potential HHF is unclear. However, the results in the current paper are very similar to those reported previously in SHIFT, in which investigators were not required to provide specific criteria either in a checklist or a narrative. At times, criteria were identified from the electronic clinical report form when they were not provided in either the source, the checklist or the narrative. This may have resulted in classifying some HHFs in the full SCTI rather than the non-SCTI category despite limited documentation. The CEC did not document specific details of whether SCTI criteria were met by source, checklist, narrative, or electronic clinical report form.

The adjudication process in EMPEROR-Reduced had similarities to other clinical trials, with 2 reviewers evaluating each event, but differed in requiring the adjudicators to agree among themselves and with the investigator; otherwise, the event would then be placed before the full committee. The data in this paper examine HF endpoints but not a comparison of myocardial infarction or stroke.

EMPEROR-Reduced was a double-blind pharmacologic treatment study in patients with HFrEF. Adjudication findings in other circumstances such as unblinded, device trials, or preserved ejection fraction HF studies may differ.

CONCLUSIONS

Our study confirms and significantly extends previous investigations comparing investigator-reported and CEC-reported events in HF trials. In this study, the investigators had a similar accuracy in detecting treatment effect and HHF events with comparable risk of fatal outcome compared to the CEC—but with more rapid accumulation of primary outcome events. This suggests little benefit provided by a central adjudication process. Our data also indicate that the recently emerging approach of requiring granular criteria for an HF event definition is unnecessary,

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because this did not improve accuracy and may delay the accumulation of events to complete a trial. Our data also raise the question whether a hospitalization should be considered an HF event when worsening HF is the primary cause of admission but also when it is present along with a different primary cause of admission. This might better reflect the spectrum of worsening disease.

In summary, these findings point toward an adjudication strategy in HFrEF that could consist of investigator-reported events or a CEC using a broader definition of hospitalization for worsening HF.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In assessing HHFs and deaths, the investigators' results provided similar accuracy to those of the CEC for detecting treatment effect and risk of subsequent fatal events after a HHF. Investigator-reported events accumulated faster than CEC-adjudicated events. For hospitalizations in which heart failure may not have been the primary cause, there was still evidence of progressing disease associated with a particularly high subsequent fatality rate.

TRANSLATIONAL OUTLOOK: The use of investigator events in a clinical trial provides a simpler method that may hasten trial completion without sacrificing accuracy. The expansion of a hospitalization definition to include "for or with" worsening heart failure disease may also hasten completion of a trial while still capturing progressing disease. These findings in a reduced ejection fraction double-blind pharmacologic study need to be evaluated further in trials with preserved ejection fraction and also devices.

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KEY WORDS adjudication, empagliflozin, heart failure, investigator

APPENDIX For an expanded Methods section as well as supplemental figures and tables, please see the online version of this paper.