Empagliflozin in patients post myocardial infarction rationale and design of the EMPACT-MI trial

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Background Patients with acute myocardial infarction (MI) are at risk for developing heart failure (HF) and subsequently are at an increased risk of mortality. Sodium-glucose cotransporter-2 inhibitors have been proven to improve outcomes in patients with HF with reduced ejection fraction, and, in the case of empagliflozin, in HF with preserved ejection fraction even without diabetes, but their efficacy and safety in the post-MI population has not yet been evaluated.

Methods The EMPACT-MI trial will evaluate the safety and efficacy of empagliflozin compared with placebo in patients hospitalized for MI with or at high risk of new onset HF, in addition to standard care. EMPACT-MI is a streamlined, multinational, randomized, double-blind, placebo-controlled trial randomizing 5,000 participants at approximately 480 centers in 22 countries. Eligible patients presenting with spontaneous MI must have new signs or symptoms of pulmonary congestion requiring treatment or new left ventricular dysfunction (LVEF<45%), and at least 1 additional risk factor for development of future HF. Eligible and consenting patients are randomized to empagliflozin 10mg or placebo daily in addition to standard of care within 14 days of hospital admission for MI. The primary composite end point is time to first hospitalization for HF or all-cause mortality.

Conclusions EMPACT-MI will inform clinical practice regarding the role of empagliflozin in patients after an MI with high-risk for the development of future HF and mortality. (Am Heart J 2022;253:86–98.)

Acute coronary syndrome (ACS) affects ~1 million individuals in the United States and up to 7 million individuals globally every year.[1-3] While many interventional and medical strategies have reduced the risk for mortality substantially in these patients, they nevertheless remain at high-risk of developing chronic heart failure (HF) and subsequently face a higher risk of mortality and disability; particularly those who present with left ventricular systolic dysfunction (LVSD) or pulmonary congestion during their index hospitalization.[4] Since the trials with angiotensin converting enzyme inhibitors (ACEi) and mineralocorticoid receptor antagonists (MRA) were completed, little progress has been made over the last decade in developing effective therapies to further reduce this persistently high residual risk. Of note, the Prospective ARNI vs ACE Inhibitor Trial to DetermIne Superiority in Reducing Heart Failure Events After MI (PARADISE-MI) trial recently reported that randomization to the angiotensin receptor-neprilysin inhibitor (ARNI) sacubitril-valsartan in patients post myocardial infarction (MI) did not significantly reduce the risk of cardiovascular (CV) death or HF events compared with ramipril.[5]

Sodium-glucose cotransporter-2 inhibitors (SGLT2is) have been shown to improve HF outcomes in patients with type 2 diabetes mellitus (T2DM), chronic kidney disease, and HF with reduced and, in the case of empagliflozin, preserved left ventricular ejection fraction

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Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARNI, angiotensin receptor-neprilysin inhibitor; ACS, Acute Coronary Syndrome; ACS-HF, Acute Decompensated heart failure in the setting of acute coronary syndrome; CV, Cardiovascular; DMC, Data Monitoring Committee; HF, Heart Failure; HHF, Hospitalization for heart failure; LVEF, left ventricular ejection fraction; LVSD, Left ventricular systolic dysfunction; MI, Myocardial infarction; SGLT2i, Sodium-glucose cotransporter-2 inhibitors; T2DM, Type 2 diabetes.

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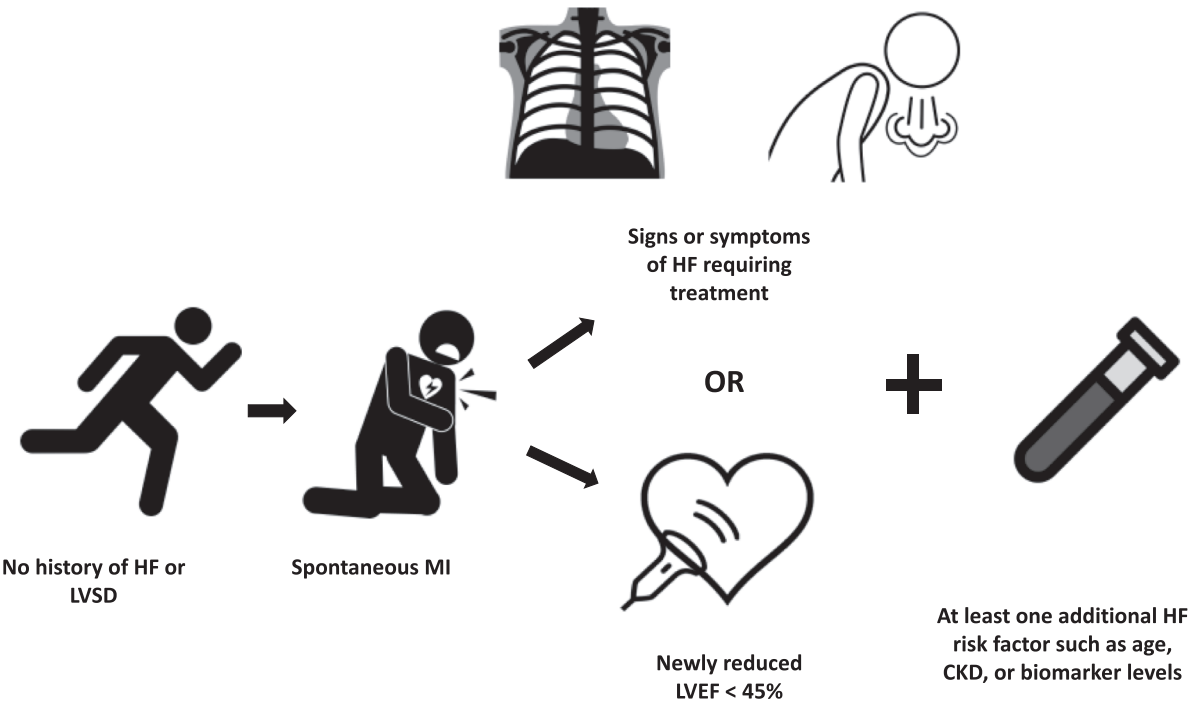
Figure 1



Major trial inclusion and exclusion features. For full list of inclusion and exclusion factors, see appendix. CKD, chronic kidney disease; HF, heart failure; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; MI, myocardial infarction

(LVEF) with or without diabetes.[6-12,12-21] One knowledge gap that remains is the safety and efficacy of this class of drugs in the post-MI population. To further understand the utility of SGLT2i in patient's post-infarction, we hypothesized that early intervention with empagliflozin after MI for patients at high risk of developing HF would reduce the risk for future mortality and hospitalizations for HF (HHF).

Overview

EMPAgliflozin on Hospitalization for Heart Failure and Mortality in Patients With aCuTe Myocardial Infarction (EMPACT-MI) is multicenter, randomized, parallel group, double-blind, placebo-controlled, streamlined trial jointly initiated by academic investigators and the sponsor to evaluate the safety and efficacy of empagliflozin 10mg daily vs placebo and standard of care in patients at high-risk for developing new onset HF after acute MI (Figure 1). This trial plans to randomize approximately 5000 patients from approximately 480 sites across North and South America, Europe, Asia, and Australia. Eligible patients are those presenting with MI and new LVSD or new signs or symptoms of HF requiring treatment with at least one additional observed risk factor for development of HF (Table I). Several design elements allow for more streamlined trial execution, including options for remote follow-up, investigator rather than adjudication committee designation of end point events, and focused safety event collection. The study will continue until the targeted number of primary end points (532) occur.

Treatment protocol and follow-up

The major inclusion and exclusion criteria of the EMPACT MI trial are shown in Table I (for full list, see appendix). Eligible patients for EMPACT-MI must provide informed consent and have had a spontaneous MI requiring hospital admission within the 14 days before randomization. Spontaneous MI is defined as MI with a primary etiology of acute coronary artery disease pathology (eg, plaque rupture/erosion, in-stent restenosis or thrombosis), rather than MI caused by supply-demand mismatch (eg, MI due to sepsis, arrhythmia, anemia, or other condition). Patients must additionally have signs or symptoms of pulmonary congestion requiring treatment, or new onset LVSD (defined as an LVEF <45%). To enrich the population for patients with higher risk of events, patients must have at least one additional risk factor (see Table I).

Patients are not eligible for participation if they have a history of chronic HF or LVSD prior to index MI, current

Table I. Overview of EMPACT-MI patient population.

Diagnosis of Spontaneous Acute MI*		Symptoms or signs of congestion requiring treatment at any time during index hospitalization		Newly developed LVEF <45%		At least one enrichment criterion
• STEMI or NSTEMI • Hospital Admission within past 14 days before randomization	AND	Symptoms (eg, dyspnea; decreased exercise tolerance; fatigue Signs of Congestion (eg, pulmonary rales, crackles or crepitations; elevated jugular venous pressure; congestion on chest X-ray), Treatment (eg, augmentation or initiation of oral diuretic therapy; iv. diuretic therapy; iv. vasoactive agent; mechanical intervention etc.)	OR	As measured by echocardiography, ventriculography, cardiac CT, MRI or radionuclide imaging during index hospitalization.	AND	- Age ≥65 years - Newly developed LVEF <35% - Prior MI - eGFR <60 ml/min/1.73m^2 - Atrial fibrillation - Type 2 diabetes mellitus - NT-proBNP ≥1,400 pg/mL for patients in sinus rhythm ≥2,800 pg/mL if atrial fibrillation; BNP ≥350 pg/mL for patients in sinus rhythm, ≥700 pg/mL if atrial fibrillation - Uric acid ≥7.5 mg/dL (≥446 μmol/L) - Pulmonary Artery Systolic Pressure (or right ventricular systolic pressure) ≥40 mmHg - Patient not revascularized (and no planned revascularization) for the index MI - 3-vessel coronary artery disease at time of index MI - Diagnosis of peripheral artery disease
No diagnosis of Chronic HF prior to index hospitalization						

*Spontaneous MI is defined as MI with a primary etiology of acute coronary artery disease pathology (eg, plaque rupture/erosion, in-stent restenosis or thrombosis). Please see appendix for full list of inclusion and exclusion criteria. CT, computed tomography; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; JVP, jugular venous pressure; MI, myocardial infarction; MRI, magnetic resonance imaging; NSTEMI, non-ST elevation MI; STEMI, ST elevation MI; T2DM, type 2 diabetes

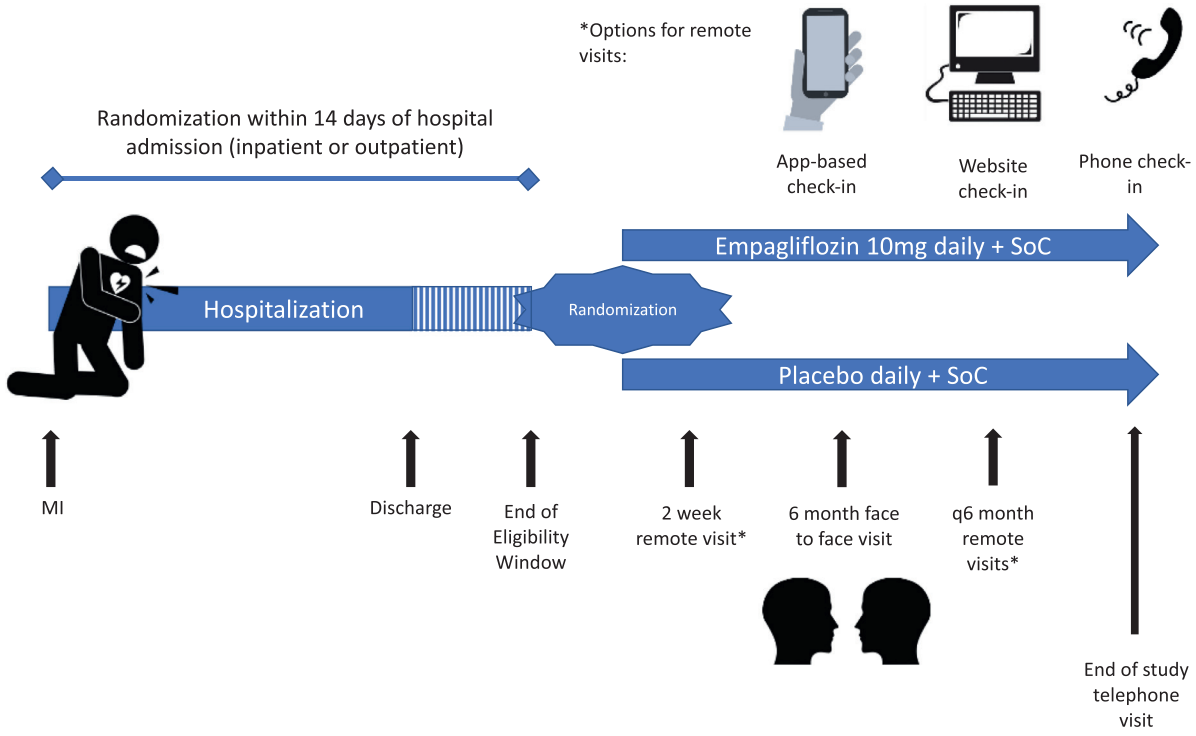
evidence of cardiogenic shock, estimated glomerular filtration rate (eGFR) <20 ml/min/1.73m^2 by the CKD-EPI formula, or if they are on dialysis. Patients are additionally ineligible if they have current or planned initiation of an SGLT2i or combined SGLT2/SGLT1 inhibitors (see appendix).

In addition to an assessment of inclusion and exclusion criteria, patient demographic and medical history will be obtained during screening, along with urine pregnancy testing in women of childbearing potential. Patients must also have an available creatinine level from their MI hospitalization; no other blood work is required. Informed consent will be obtained, along with a patient preference for mode of follow-up during remote visits, including options for internet, web-based app, or telephone follow-up (Figure 2).

Though investigators are encouraged to randomize patients during the index hospitalization for MI, patients may be randomized as inpatients or outpatients for up to 14 days after hospital admission. Upon completion of the screening period, patients receive an in-person visit, including physical exam and final review of inclusion/exclusion criteria, undergo randomization, and receive study drug. Patients will have a remote visit at 2 weeks and a face-to-face visit at 6 months after randomization. Thereafter patients will have a remote visit every 6 months for the duration of the trial. During these visits, adherence to the medication, adverse events and end points will be assessed, along with specific concomitant medications. Study drug resupply will be provided at follow up either in person or via remote delivery when permitted. At the end of study, a final telephone visit will assess adherence, study end points as well as serious adverse events, adverse events of special interest, and adverse events leading to study drug discontinuation.

Any patient who misses an app- or web-based check-in will be contacted by their site, and patients who are unresponsive will be reached out to several times in an effort to minimize loss to follow-up. Any concerns, including possible end point or adverse event occurrence or study drug adherence concerns identified during remote follow-up will prompt a telephone visit for more information. At any point a patient or investigator can conduct an on-site visit, either in lieu or in addition to a planned remote visit. As this trial is being conducted during the global COVID-19 pandemic, and patients with CV disease are known to be at a heightened risk for complications related to COVID-19, should local conditions preclude face-to-face visits, remote visits can be substituted as needed if this is judged necessary to protect patient and staff safety. All participants involved in trial conduct and analysis, including patients and investigators, will re-

Figure 2



Randomization and Follow-up Schedule and Options. MI, myocardial infarction; SoC, standard of care

Table II. Primary and secondary end points in EMPACT-MI.

Primary end point	Composite of time to first HHF or all-cause mortality
Secondary End points	*Key Secondary End points*
	Total number of HHF or all-cause mortality
	Total number of non-elective CV hospitalizations or all-cause mortality
	Total number of non-elective all-cause hospitalizations or all-cause mortality
	Total number of hospitalizations for MI or all-cause mortality
	Exploratory Secondary End points
	Time to CV mortality

CV, cardiovascular; HHF, hospitalization for heart failure; MI, Myocardial infarction

main blind to treatment assignments until after database lock occurs. The Data Monitoring Committee (DMC) will have access to unblinded data for safety reviews to occur.

Study End points and Safety Events

The primary end point for EMPACT-MI is the composite of time to first HHF or all-cause mortality (Table II). Key secondary end points are total number of HHF or all-cause mortality, total number of non-elective CV hospitalizations or all-cause mortality, total number of non-elective all-cause hospitalizations or all-cause mortality, and total number of hospitalizations for MI or all-cause mortality. Other secondary end points include time to CV mortality. Death will be categorized as CV or non-CV by the investigators. CV death will include mortality related to HF, sudden cardiac death, acute MI, or other CV events. EMPACT-MI has a focused safety reporting approach. To that end, safety event collection is focused on serious adverse events, adverse events leading to discontinuation of trial medication for at least 7 consecutive days, and adverse events of special interest. Adverse events of special interest are contrast-induced acute kidney injury, ketoacidosis, hepatic injury, or events leading to lower limb amputation.

End point and safety event assessment

In lieu of a central adjudication committee, blinded investigators will review all end points and events. All investigators receive training in event review as a prerequisite for trial qualification. This training includes instruc-

tion on the accurate assessment and documentation of clinical end points, adverse and serious adverse events, and adverse events of special interest.

Statistical considerations

Randomization is stratified by diabetes status and geographical region, with a 1:1 randomization ratio for empagliflozin versus placebo. The primary efficacy analysis will be based on all randomized patients. Analyses will be performed according to the intention-to-treat principle, with the use of all available data until trial end, equating a treatment-policy estimand. Patients who do not have an event during the trial will be censored at the individual day of trial completion or the last day that the patient was known to be free of the event, whichever is earliest. The difference between the placebo and empagliflozin group for the primary end point will be analyzed using a Cox proportional hazards model with treatment and pre-specified baseline covariates of T2DM, geographical region, age, eGFR category (<45, 45-<60, 60-<90, ≥90ml/min/1.73m^2 using the CKD-EPI formula), LVEF category (<35%, ≥35%) persistent or permanent atrial fibrillation, prior MI, peripheral artery disease at baseline, and smoking.

Key secondary end points will be analyzed in a hierarchical testing procedure to preserve the overall type I error rate at $\alpha = 5\%$ (two-sided). If the primary end point null hypothesis (no difference in risk between empagliflozin and placebo) is rejected, and superiority for empagliflozin is shown, a Hochberg step-up procedure [22] will be applied to test the family of 2 key secondary end points of total number of HHF or all-cause mortality and total number of non-elective CV hospitalizations or all-cause mortality. If the null hypotheses for both key secondary end points are rejected and superiority for empagliflozin is shown, then the third key secondary end point of total number of non-elective all-cause hospitalizations or all-cause mortality will be tested at $\alpha = 5\%$. The fourth key secondary end point, total number of hospitalizations for MI or all-cause mortality will be tested subsequently, if all the null for the primary and key secondary end points 1, 2 and 3 have been rejected and all show superiority of empagliflozin versus placebo. If a null hypothesis cannot be rejected, the hierarchical testing procedure will be stopped, and all subsequent hierarchical testing considered exploratory.

Kaplan-Meier curves and non-parametric mean cumulative function curves will be used for graphical presentation. Safety analyses will be performed on the treated set, including patients who were treated with at least 1 dose of study medication. The primary and key efficacy end points will be also evaluated in a number of subgroup analyses according to the baseline factors including T2D status, age, geographic region, sex, race, LVEF, eGFR. Further additional and subgroup analyses of the trial will be prespecified in the Trial Statistical Analysis Plan before Database Lock.

EMPACT-MI is an event-driven trial and will continue until at least 532 primary outcome events are observed. With this, the trial has 85% power to show a 23% risk reduction for the primary end point based on a type I error rate of 5% (two-sided α). Assuming a yearly event rate of 12.5% in the placebo group, a yearly drop-out rate of 1%, 12 months of recruitment and an additional estimated 12 months of follow-up, the original clinical trial protocol planned to randomize 3,312 patients to achieve the 532 events.

During trial conduct the recruitment progress was slower than initially planned and associated event accumulation was slower than anticipated. Therefore, the decision was taken to increase the sample size to 5,000 patients based on blinded study data to avoid a substantial prolongation of overall study duration. This increase of patient number also prompted an increase in recruitment period to estimated 21 months with additional follow-up for an estimated 5 months until 532 primary events have occurred. The protocol allows further increase of sample size up to 6,500 patients if accrual of primary outcome events over calendar time is slower than originally expected. No interim efficacy analyses are planned.

Funding and study organization

EMPACT-MI is sponsored by Boehringer Ingelheim in collaboration with Eli Lilly, with trial coordination through the Duke Clinical Research Institute (Durham, NC). An Executive Committee, made up of leaders in heart failure and coronary disease, as well as sponsor representatives provide expert opinion in trial design and execution. A Steering Committee includes representation from experts from each participating country and will also support trial execution in an advisory capacity. Overall trial responsibility lies with the Executive Committee, which is made up of a multinational group of thought leaders and sponsor representatives (Appendix).

A Data Monitoring Committee (DMC) is made up of independent physicians with expertise in diabetes, HF and ACS, as well as a statistician (Appendix). The DMC meets quarterly to review unblinded data for safety concerns, with measures in place to ensure that blinding is maintained for other trial members. The DMC is responsible for recommendations regarding the continuation, termination, or amendment of the trial based on their safety analyses. These recommendations, and the final sponsor decision, are reported to all regulatory bodies as well as institutional review boards and the executive committee.

The authors are fully responsible for all content and editorial decisions, were involved in all stages of manuscript development and approved the final version.

Ethical considerations

EMPACT-MI is designed in accordance with the Declaration of Helsinki and the International Council for Harmonization Guidelines for Good Clinical Practice, as well as relevant Boehringer Ingelheim standard operating procedures, the European Union's directive 2001/20/EC and regulation 536/2014, and all other relevant regulations. In accordance with national and international regulations, all respective institutional review boards and regulatory authorities must review and approve the protocol prior to trial initiation at a given site and written informed consent must be obtained from every study participant before their enrollment.

Discussion

The ongoing EMPACT-MI trial is a streamlined, multicenter, randomized, double-blind trial designed to assess the efficacy and safety of empagliflozin compared with placebo in addition to standard of care in patients with either new LVSD (LVEF<45%) or new signs or symptoms of HF requiring treatment following acute MI. The primary aim of the study is to assess the reduction in the risk for the composite end point of time to first HHF or all-cause mortality. The study population will be enriched for patients at high risk for CV death or HHF by way of at least one additional cardiovascular risk factor.

SGLT2is have proven to be beneficial for reducing the risk of CV death and HHF across a wide spectrum of patients. In patients with T2DM, empagliflozin and other SGLT2is are known to improve these outcomes in both patients with and without a previous history of heart failure.[7-9,11,12,14] More recently, SGLT2is, including empagliflozin, have been shown to reduce HHF and CV death not only in patients with T2DM, but also in patients with chronic HF, both with reduced and, in the case of empagliflozin, preserved ejection fraction, regardless of diabetes status [7,8,15]. The recent finding that empagliflozin is effective in reducing HHF in patients with HF with preserved ejection fraction may be especially important. Though LVSD is a known risk factor for death and HHF after ACS, patients with new signs or symptoms of HF requiring treatment but without LVSD will be also included in our study. It should also be noted that the recently completed PARADISE-MI trial, which did not find a difference in outcomes in patients randomized to sacubitril-valsartan vs ramipril with acute HF after MI, also included patients with preserved EF. Though further analyses are needed, this lack of benefit may have been related to the previously neutral findings from the Multicenter, Randomized, Double-blind, Parallel Group, Active-controlled Study to Evaluate the Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients (NYHA Class II-IV) With Preserved Ejection Fraction (PARAGON-HF) trial, which found that sacubitril-valsartan did not significantly lower rates of death or HHF compared with valsartan alone.[23] However, given the significant benefit associated with sacubitril-valsartan in patients with both chronic and acute HF with reduced ejection fraction,[24,25] these discordant findings also emphasize the fact that acute congestion and/or LVSD following an MI is not necessarily the same as chronic or even other forms of *de novo* HF. As prior clinical trials of SGLT2is have excluded patients with acute or recent MI, the efficacy of these drugs in mitigating future CV risk in a post-MI population requires dedicated investigation.

Increasingly, there has been an emphasis on the integration of real-world evidence and more pragmatic trial design elements into study design and execution.[26] Such efforts aim to make trials more efficient, while simultaneously increasing the likelihood that trial results be maintained in real-world clinical settings.[27,28] To this end, EMPACT-MI will incorporate pragmatic trial elements by using inclusion and exclusion criteria readily available in the course of standard clinical care, conducting remote follow-up for some visits, performing focused safety collection, and using a blinded investigator event review in lieu of an adjudication committee. This trial design is enabled by the preponderance of data available for empagliflozin.

Empagliflozin already has a well-established safety record in patients with or at high risk for CV disease.[8,9,15,29,30] This well-established safety facilitates patient research visits to be conducted remotely and enables a more efficient collection of safety data emphasizing events that are serious, or of particular interest, or that lead to study drug discontinuation. Through focused end point collection, it is possible to use blinded investigator end point review instead of a central adjudication committee. Adjudication in HF trials does not appear to enhance quality or robustness of data, and recent analyses have reported high concordance between investigator and clinical event committee (CEC)-adjudicated events, and suggests that CEC adjudication is likely not necessary for all clinical trials, especially those that are randomized and blinded, with hard and objective end points.[12,31-33] In addition to being highly qualified clinically, investigators in EMPACT-MI will receive specialized training and, importantly, be blinded to study drug randomization. The use of investigator end point review is also enabled by the use of hard and objective end points with clearly defined criteria and structured collection of end point data. Use of source data verification will serve as an additional quality metric.

The use of focused collection of safety events also makes it possible to make follow-up visits remote, because there are no required in-trial blood draws, physical exams or required on-site activities. The embedded remote visits reduce the time demands placed on the patient, which may make enrollment easier. Consequently, these pragmatic trial elements will allow for inclusion of

a broader patient population, including those who live further from the enrolling site, and maintain external validity of trial results.[34] These remote research visits include a structured questionnaire that depending on patient preference, can be completed through an app, website, or by phone. This also significantly reduces the burden on the enrolling site's clinical research coordinators, helping to make the trial more efficient to conduct. In the era of COVID-19, the ability to conduct remote visits is also essential to protecting both patients and research coordinators, while simultaneously preserving trial viability.

There is a chance that providers faced with the recent positive findings of the EMPULSE, EMPEROR-Preserved and EMPEROR-Reduced trials may choose to initiate open-label empagliflozin for their patients with HF symptoms and/or LVSD after MI, which would preclude their enrollment in this trial,[15,35,36] despite a dearth of evidence on efficacy of SGLT-2 inhibitors in a post-MI patient population. However, given the historically slow uptake of research findings into clinical practice, and the fact that <10% of eligible patients are currently on an SGLT2i, we do not anticipate that this will significantly impact our trial [37-39]. Nevertheless, should an investigator feel at any point that a patient would clearly benefit from an SGLT2i, then they could discontinue study drug and begin treatment with an open-label SGLT2i, with continued follow-up of the patients until end of study. Though we anticipate that such crossover is most likely to occur following an event such as HHF, we will assess for trends in study drug discontinuation and start of non-study drug SGLT2i over the course of the study. The study design is setup in a way to be able to handle a cross-over rate from study drug to non-study drug SGLT-2 inhibitor of up to 12.5%. The primary analysis of the trial uses all available data according to the ITT principle, including all data after cross-over to non-study drug SGLT-2 inhibitor. Sensitivity analyses are prespecified to investigate the effect of this cross-over. Current or planned use of SGLT2i is additionally an exclusion criterion for EMPACT-MI, such that any patient felt to have a clear indication for SGLT2i by their provider prior to enrollment would not be considered eligible for the trial.

In conclusion, there is a significant unmet need for new and effective therapies in patients with acute MI and high-risk of HF. SGLT2is have established benefit for patients with or at high-risk for CV disease, regardless of diabetes status, but evidence of efficacy and safety for this class following acute MI is lacking. EMPACT-MI will therefore evaluate the safety and efficacy of empagliflozin vs placebo in addition to standard care in patients at high risk for HF or mortality following MI

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Inclusion Criteria for EMPACT-MI

- Of full age of consent (according to local legislation, at least 18 years) at screening.
- Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial.
- For women of childbearing potential, must be ready and able to use highly effective birth control with a low failure rate of <1% per year when used consistently and correctly.
- Diagnosis of acute spontaneous* NSTEMI or STEMI, with randomization to occur no later than 14 calendar days after hospital admission. For patients with in-hospital MI as qualifying event, randomization must still occur within 14 days of randomization.
- High risk of HF, defined as either:
  - Symptoms (eg, dyspnea, fatigue, decreased exercise tolerance) *or* signs of congestion (eg, pulmonary rales, crackles, crepitations, elevated jugular venous pressure, congestion on CXR) *requiring treatment* (augmentation or initiation of oral diuretic therapy, iv diuretic therapy, IV vasoactive agent, mechanical intervention) during hospitalization

  Or
  - Newly developed LVEF <45% as measured by echocardiography, ventriculography, cardiac CT, MRI, or radionuclide imaging during index hospitalization

- At least one of the following risk factors:
  - age ≥65 years
  - newly developed LVEF <35%
  - prior MI (before index MI) documented in medical records
  - eGFR <60 ml/min/1.73 m^2 (using CKD-EPI formula based on creatinine from local lab, at any time during index hospitalization
  - Atrial fibrillation (persistent or permanent; if paroxysmal, only valid if associated with index MI)
  - Prior or new diagnosis of T2DM
  - NT-proBNP ≥1,400 pg/mL if in sinus rhythm, ≥2,800 pg/mL if in atrial fibrillation; BNP ≥350 pg/mL if in sinus rhythm, ≥700 pg/mL if in atrial fibrillation, measured at any time during hospitalization.
  - Uric acid ≥7.5 mg/dL (≥446 μmol/L), measured at any time during hospitalization
  - Pulmonary artery systolic pressure (or right ventricular systolic pressure) ≥40mmHg (measured non-invasively, typically in clinically indicated post-MI echocardiography) or invasively, at any time during hospitalization
  - Patient not revascularized (and no planned revascularization for index MI (includes patients with no angiography performed, unsuccessful revascularization attempts, diffuse atherosclerosis not amenable to intervention, but does NOT include patients for whom no revascularization was performed due to non-obstructive coronary artery disease).

- 3-vessel coronary artery disease at time of index MI.
- diagnosis of peripheral artery disease (extracoronary vascular disease such as lower extremity artery disease or carotid artery disease).

1. *CT: computed tomography; CXR: chest Xray; EF: ejection fraction; eGFR: estimated glomerular filtration rate; HF: heart failure; IV: intravenous; JVP: jugular venous pressure; MI: myocardial infarction; MRI: magnetic resonance imaging; NSTEMI: non-ST elevation MI; STEMI: ST elevation MI; T2DM: type 2 diabetes.*
2. * *Spontaneous MI is defined as MI with a primary etiology of acute coronary artery disease pathology (eg, plaque rupture/erosion, in-stent restenosis or thrombosis), rather than MI caused by supply-demand mismatch (eg, MI due to sepsis, arrhythmia, anemia, or other condition).*

Exclusion criteria for EMPACT-MI trial

- Diagnosis of chronic HF prior to index MI.
- Systolic blood pressure $\leq$ 90 mmHg at randomization.
- Cardiogenic shock or use of IV inotropes in last 24 hours before randomization.
- Coronary artery bypass grafting planned at time of randomization.
- Current diagnosis of Takotsubo cardiomyopathy.
- Any current severe (stenotic or regurgitant) valvular heart disease.
- eGFR<20 ml/min/1.73m^2 (using CKD-EPI formular based on most recent creatinine from local lab during index hospitalization), or on dialysis.
- Type 1 diabetes mellitus
- History of ketoacidosis
- Current or planned treatment with an SGLT2i or combined SGLT1 and 2 inhibitors. Discontinuation of an SGLT2i or combined SGLT1 and 2 inhibitors for the purposes of enrollment in the trial is not permitted.
- Contraindication for use of empagliflozin or any other SGLT2i
- Any physical or mental condition significantly affecting the patient's ability to participate in the Investigator's opinion.
- Any other clinical condition that would jeopardize patient safety while participating in this study, or that might prevent the patient from adhering to the trial protocol in the Investigator's opinion.
- Presence of any other disease than the acute MI or its immediate complications with a life expectancy of <1 year in the opinion of the investigator.
- Current or previous randomization in one of the empagliflozin heart trials, or currently enrolled in another investigation device or drug trial, or less than 30 days since end another investigational device or drug trial, or receiving other investigational treatment(s).
- Women who are pregnant, nursing, or who plan to become pregnant while in the trial

BP: blood pressure; eGFR: estimated glomerular filtration rate; IV: intravenous.

Definition of end points evaluated in the EMPACT-MI trial

There is no centralized event adjudication in EMPACT-MI. Instead, the verification of outcomes of interest will rely on the assessment of the blinded investigators. This process is characterized by event collection by review of hospital records and consistently asking participants about events; thorough investigator review and assessment of available source documentation; and ultimately recording of end point specific data in the structured eCRF.

All EMPACT-MI investigators have been trained on the trial end points definition provided below and this information is available at every site.

Deaths

All-cause mortality is a component of the primary composite end point; therefore, any reported death will be included in the analysis. Similar to traditional clinical studies, investigators are asked to judge and report the most likely cause of death. For all deaths, sites should collect and investigators review all available information including hospital records (discharge or death summaries), death certificates, autopsy reports and reports from potential witnesses and relatives. Investigators should then use this information to confirm and report the primary cause of death using the convention "If not for (blank), the participant would still be alive", in which case (blank) would be the cause of death. For in-hospital deaths where the primary cause cannot be easily determined by any of the below descriptions, usually the cause of hospital admission would also be the primary cause of death.

The following death subcategories are reported in the eCRF:

- Cardiovascular (CV) death
  - Acute myocardial infarction
    - ☐ Typically, death due to acute MI is any death within 30 days after a confirmed MI if related to the immediate consequences of the MI (eg, deaths due to heart failure, sudden cardiac death following acute MI).
    - ☐ Acute MI should be verified with source data (hospitalization summary, troponin values, and/or autopsy) and there should not be other explanations for death (eg, trauma, non-CV causes).

☐ In the event that patients present with symptoms of acute MI, have ECG/angiography/autopsy evidence of acute MI, but do not have troponin assays, these deaths should be classified as due to acute MI.

○ Sudden Cardiac Death

☐ Sudden cardiac death is defined as any death that occurs unexpectedly.
☐ Witnessed deaths occurring without any new or worsening symptoms; or within 60 minutes of new or worsening symptoms (but not consistent with acute MI as above).
☐ Unwitnessed deaths where patient was seen alive and clinically stable <24 hours and there is no evidence supporting other likely cause.
☐ Any death after unsuccessful resuscitation from cardiac arrest and without other specific CV- or non-CV cause specified in this document (ie, known MI, HF, other CV or non-CV death).

○ Heart Failure

☐ Death associated with clinically worsening symptoms and/or signs of heart failure (regardless of HF etiology) and also includes deaths that result from complications of treatments for heart failure (eg, LVAD, heart transplant).
☐ Deaths that occur during a heart failure hospitalization will generally be attributed to heart failure, even if there is another immediate CV cause of death (eg, ventricular fibrillation).
☐ Deaths that occur in hospice or other similar palliative care setting for heart failure should be attributed to heart failure.

○ Other CV Causes

☐ Death due to Other CV Causes include any deaths with cardiovascular cause other than sudden cardiac death, MI or HF; including stroke, CV procedure, CV hemorrhage etc. There is no subclassification of other CV Causes of death.

- *Non-CV death*: there is no subclassification of non-CV death.

- Unknown cause of death

○ Uncertainty can remain after review of available evidence, and while rare, Unknown Cause of Death should only be selected in cases where minimal or no information related to the death is available to determine a likely cause. In order to minimize the selection of Unknown Cause of Death, sites should make every effort to gather source data (when it exists) and narratives from family members/friends/neighbors.

Hospitalizations

Hospitalizations are key end points in EMPACT-MI. All hospitalizations are to be collected and reported during the trial. To qualify as a hospitalization, the hospital stay must include at least 1 date change (ie, at least 1 overnight stay) to be analyzed as a hospitalization. For all hospitalizations, admission and discharge date and information on whether elective or non-elective will be collected. For certain end points specified in the trial protocol, only the non-elective hospitalizations will be analyzed. These are HHF as part of primary and key secondary end points, CV, and all cause hospitalizations as part of key secondary end points.

Hospitalization for Heart Failure (HHF)

HHF is one of the components of the primary end point. Detailed information related to these events is collected on the Hospitalization page. For analysis as a HHF in EMPACT-MI (for primary and key secondary end points), hospitalizations need to be non-elective with a primary cause of heart failure, defined as at least 1 heart failure symptom or sign (lab and imaging findings are considered as signs) requiring treatment (eg, diuretics, inotropes, mechanical circulatory support).

To ensure that all HHF events are properly captured it is critical that sites obtain supporting source documentation, likely to include the above information. At minimum, this typically includes the admission note and discharge summary but additional supporting information can be found in progress notes, procedure reports (eg, right heart catheterization report), laboratory data (eg, BNP or pro-NT BNP), and other medical notes.

HHF components

- Non-elective/unplanned: The designation of non-elective/unplanned is typically referenced in the source data. Examples of non-elective/unplanned include:

  • Hospitalization from emergency department
  • Hospitalizations where patient is admitted directly to the ICU/medical ward from home due to worsening HF
  • Hospitalizations where patient is admitted directly to the ICU/medical ward from outpatient clinic due to worsening HF

- Symptoms, including all symptoms that were related to HF, which lead to hospitalization. If a symptom of HF is not represented in the preselection, option 'Other' can be selected.
- Signs, includes either physical or lab/imaging findings consistent with HF:

  • Physical signs related to HF, typically evident at presentation or early during the hospitalization. If

a sign of HF is not represented in the eCRF preselection, option 'Other' can be selected.
- Lab/imaging findings consistent with worsening HF, incl elevated natriuretic peptides, radiological evidence of congestion etc. Lab/imaging findings are not always available immediately upon admission (for instance chest x-ray performed day after admission). If a lab/imaging finding corresponding to HF is not represented in the preselection, option 'Other' can be selected.

- Treatment: includes any of the defined treatments for worsening HF (ie, initiated or intensified oral or iv diuretics, other iv HF therapies, mechanical fluid removal or circulatory support) administered during the hospitalization.

Hospitalization for myocardial infarction

Hospitalization for MI is a component of a key secondary end point. These are hospitalizations with a primary cause of acute myocardial infarction, defined according to prevailing guidelines. Given the acute nature of this hospitalization, it should never be recorded as 'elective'. In the eCRF, it will further be classified as either non-ST elevation MI or ST-elevation MI based on best available source documentation (eg, ECG, medical notes/discharge summary).

Hospitalization for any other CV reason

A hospitalization with a primary cause as 'any other CV' encompasses hospitalizations with a primary CV reason other than HF or MI. This includes, but is not limited to, ischemic heart disease (other than MI), arrhythmias, valvular heart disease, aortic dissection or rupture, peripheral artery disease events and pulmonary embolism.

Hospitalization for non-CV reason

Any hospitalization that does not meet the criteria for HF, MI or any other CV hospitalization and has a non-CV reason as the primary cause for hospitalization.

Other specific events/procedures

In addition to death and hospitalization, a few additional events/procedures need to be collected and recorded on the Concomitant Non-drug Therapy page. These are to be recorded irrespective of whether they were part of a hospitalization or not, and include:

- myocardial revascularization procedures (percutaneous coronary intervention or coronary artery bypass grafting)
- cardiac device procedures (implantable cardioversion defibrillator or cardiac resynchronization therapy)
- renal replacement therapy/dialysis and renal transplantation

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