Rationale and design of the DAPA-MI trial: Dapagliflozin in patients without diabetes mellitus with acute myocardial infarction

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Abstract

Background Therapies that could further prevent the development of heart failure (HF) and other cardiovascular and metabolic events in patients with recent myocardial infarction (MI) represent a large and unmet medical need.

Methods DAPA-MI is a multicenter, parallel-group, registry-based, randomized, double-blind, placebo-controlled phase 3 trial in patients without known diabetes or established HF, presenting with MI and impaired left ventricular systolic function or Q-wave MI. The trial evaluated the effect of dapagliflozin 10 mg vs placebo, given once daily in addition to standard of care therapy, on death, hospitalization for HF (HHF), and other cardiometabolic outcomes. The primary objective of the trial was to determine, using the win-ratio method, if dapagliflozin is superior to placebo by comparing the hierarchical composite outcome of death, HHF, nonfatal MI, atrial fibrillation/flutter, new onset of type 2 diabetes mellitus, HF symptoms as measured by New York Heart Association Functional Classification at last visit, and body weight decrease $\geq$5% at last visit. Assuming a true win-ratio of 1.20 between dapagliflozin and placebo, 4,000 patients provide a statistical power of 80% for the test of the primary composite outcome. A registry-based randomized controlled trial framework allowed for recruitment, randomization, blinding, and pragmatic data collection of baseline demographics, medications, and clinical outcomes using existing national clinical registries (in Sweden and the UK) integrated with the trial database.

Conclusions The trial explores opportunities to improve further the outcome of patients with impaired LV function after MI. The innovative trial design of DAPA-MI, incorporating national clinical registry data, has facilitated efficient patient recruitment as well as outcome ascertainment.

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With a gradual implementation of new, effective, and guideline-supported myocardial infarction (MI) treatments, such as percutaneous coronary intervention (PCI), dual antiplatelet therapy, statins, and angiotensin-converting enzyme (ACE) inhibitors, the overall prognosis following MI has substantially improved over time.[1-3] However, with limited new treatment options, improvements in MI prognosis have slowed in recent years. Therefore, new treatments are needed to further improve the management of patients with MI to prevent recurrent cardiovascular (CV) events.

Large clinical trials involving patients with and without type 2 diabetes mellitus (T2DM) have demonstrated sodium-glucose co-transporter-2 (SGLT2) inhibitors to be of benefit in patients with established heart failure (HF) by reducing recurrent hospitalization for HF (HHF) and other CV events. This benefit was first shown in pa-

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tients with T2DM at high risk for, or with established atherosclerotic CV disease.[4,5] In a prespecified subgroup analysis of patients with T2DM and a history of MI in the Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) trial, treatment with dapagliflozin also reduced the risk of the composite of MI, ischemic stroke, or CV death.[6] Large trials have confirmed that SGLT2 inhibition constitutes an effective and generally safe treatment option for the treatment of patients with and without T2DM with established HF and with both reduced and preserved ejection fraction, preventing deterioration in HF and CV death.[7-10] Furthermore, a pooled analysis demonstrated that dapagliflozin reduced the risk of death from CV causes across the range of ejection fraction in patients with established HF.[11] In a double-blind trial of 476 patients with acute MI accompanied by a large creatine kinase elevation (>800 IU/L), the reduction in NT-proBNP levels over 26 weeks was significantly greater with empagliflozin 10 mg daily compared with placebo.[12] In that study, left ventricular ejection fraction was around 50% at baseline and there was a significantly greater improvement in the active treatment group, together with lower left-ventricular end-systolic and end-diastolic volumes.

The DAPA-MI trial was initiated in December 2020 to evaluate the effect of treatment with dapagliflozin in patients hospitalized for MI with impaired left ventricular systolic function or Q-wave MI but without known diabetes mellitus or chronic symptomatic HF with a prior HHF within the last year and known reduced ejection fraction with indication for SGLT2 inhibition. The primary trial objective was to determine whether dapagliflozin 10 mg once daily (QD) is superior compared with placebo, when added to standard of care (SoC).

Methods

Design

DAPA-MI is a multicenter, parallel-group, registry-based, randomized, double-blind, placebo-controlled phase 3 trial. The trial enrolled patients without known diabetes or established HF presenting with MI to evaluate the effect of dapagliflozin 10 mg vs placebo, given once daily, for the prevention of death, HHF, or other adverse HF and cardiometabolic outcomes. In addition to the trial treatment, patients received SoC including specific guideline-recommended pharmacologic MI therapies (lipid-lowering therapies, antiplatelet medications, beta-blockers, renin-angiotensin system blockers, and mineralocorticoid-receptor antagonists) and advice on lifestyle interventions aimed at smoking cessation, optimal blood pressure (BP) control, diet, weight control, and physical activity. The trial was conducted within the context of routine clinical practice utilizing 2 national population-based health quality registries for patient characterization: (1) the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART)[13] and (2) the United Kingdom-based National Institute for Cardiovascular Research (NICOR) registries including the Myocardial Ischaemia National Audit Project (MINAP).[14] On top of the daily 10-mg dose of dapagliflozin or placebo, all patients were treated according to regional and international standards of care for MI.

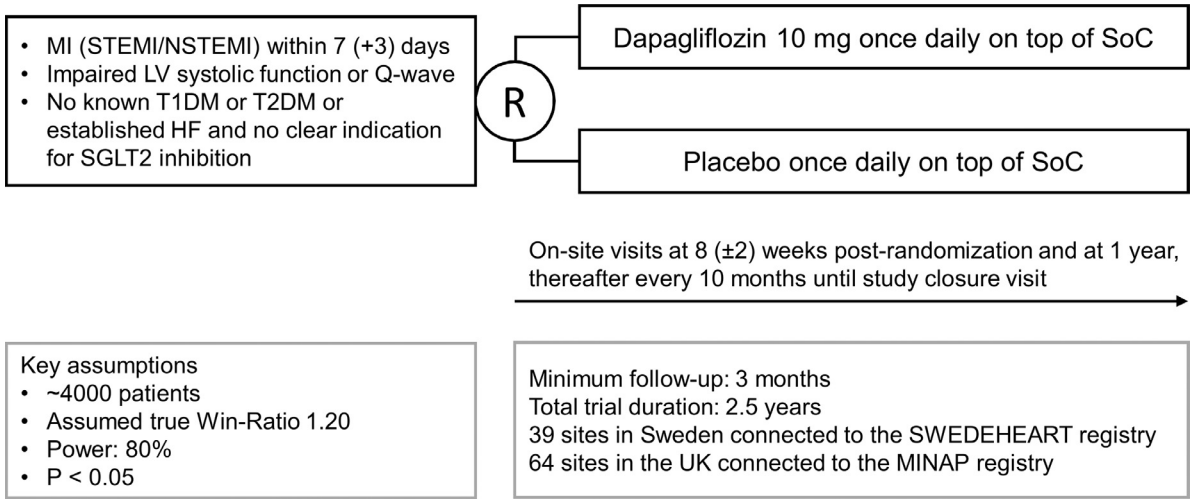
The registry-based randomized controlled trial (R-RCT) framework allowed for recruitment, randomization, blinding, and pragmatic data collection using existing clinical registry data with readily available trial infrastructure facilitating collection of baseline demographics, medications, and outcomes. The trial was conducted at 39 sites in Sweden and 64 sites in the United Kingdom (UK). Patients were enrolled from December 2020 until March 2023. The anticipated minimum trial follow-up was 3 months while the total trial period, and maximum follow-up, was 2.5 years. An overview of the trial is presented schematically in Figures 1 and 2.

The DAPA-MI trial was funded by AstraZeneca. The authors are solely responsible for the trial design, conduct of the trial, and drafting and editing of the manuscript and its final content.

Trial population

Potential participants in the DAPA-MI trial were defined as adult patients hospitalized for acute MI, including ST- or non-ST-elevation MI (STEMI or NSTEMI). Patients were recruited within cardiology departments in the UK and Sweden and entered in the SWEDEHEART or MINAP registries. They had to be clinically stable with no episodes of symptomatic hypotension or arrhythmia with hemodynamic compromise in the last 24 hours at trial enrollment, and treated with standard therapies for MI according to established international and local guidelines. Patients were eligible if, in addition to acute MI, they had imaging evidence of any degree of impaired regional or global LV systolic function during their index hospitalization, or had evidence of transmural MI by the presence of pathologic Q-waves on electrocardiogram (ECG). Coronary angiography or coronary intervention was not part of the eligibility criteria but patients were generally managed invasively according to routine clinical practice. A diagnosis of diabetes mellitus, type 1 or type 2, at the time of admission for the index event was an exclusion criterion for the trial. Patients with chronic symptomatic HF with an HHF within the last year and known reduced left ventricular ejection fraction (LVEF $\leq$ 40%) were excluded, as these patients have an absolute indication for SGLT2 inhibitor treatment. Patients currently on treatment, or with an indication for treatment, with an SGLT2-inhibitor were excluded. (For further inclusion and exclusion criteria, see Table 1.) Participation in the trial was voluntary and all potentially eligible patients re-

Figure 1



Trial outline. *MI*, myocardial infarction; *MINAP*, Myocardial Ischaemia National Audit Project; *SoC*, standard of care; *STEMI/NSTEMI*, ST- or non-ST elevation MI; *SWEDEHEART*, Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies; *T1DM*, type 1 diabetes mellitus; *T2DM*, type 2 diabetes mellitus.

ceived all relevant information on the trial treatment and procedures to facilitate their decision on whether or not to participate. The trial was conducted in accordance with the Declaration of Helsinki and International Council on Harmonisation-Good Clinical Practice (ICH-GCP) principles and was approved by the Ethical Review Authority of each country.

Trial procedures

If they met all inclusion and none of the exclusion criteria, volunteered to participate, and signed the informed consent form, patients were randomized during their index hospitalization or immediately thereafter, within 7 days from the index MI event, or within 10 days if earlier randomization was not feasible. Patients were centrally assigned to the trial treatment using a computerized randomization functionality web service supported by the R-RCT framework. Randomization was stratified by country (Sweden and the UK) and assigned the participants 1:1 to dapagliflozin or matching placebo. The treatment allocation generated within the R-RCT framework automatically and blindly provided the investigators with the kit identification number of the trial drug to be allocated to the patient at each dispensing visit (Figure 2), thus allowing the trial to be blinded to both patients and the investigators/site staff. After randomization, the patient received the trial medication and instructions to take one tablet daily (10 mg dapagliflozin or matching placebo). For follow-up, the patient visited the clinic at week 8 (±2 weeks) and month 12 (±1 month) after hospital discharge. Thereafter, the follow-up visits continued every 10 months.

Trial intervention monitoring

Adherence to randomized treatment was monitored using "smart pill bottle" technology. The trial treatment bottles containing dapagliflozin or matching placebo were fitted with the CleverCap Lite technology, a system that can provide the date and time of every bottle access. Data from the CleverCap Lite was pushed to a central portal using the 3G network. Unexpected user patterns prompted automated email notification to the trial site personnel to follow up the patient.

The Unify mobile software application

The Unify mobile software application was used during the trial to provide digital support to patients. In addition to educating the patients about lifestyle interventions, the system provided information and tools relevant to the conduct of the trial. This comprised treatment medication reminders, clinical visit reminders, and educational content relating to the disease and medication. Because it was considered an additional support tool, patients could choose not to use the application without it affecting their involvement in the trial.

To aid health technology assessment and health economic modeling, the application was also used to collect answers for the Euro Quality of Life 5 Dimensions (EQ-5D-5L) questionnaire, which patients were asked to complete 3 days after discharge and every month until their individual closing visit.

Figure 2

	Screening	Randomization	Follow-up		
	Within 7 days (+3 days) after MI	Day 1 (within 7 (+3) days from MI)	Week 8 (± 14 days)	Year 1 (±1 month)[a]	Month 22, then every 10 months (±1 month)
Informed consent	X				
Inclusion/exclusion criteria		X			
Dapagliflozin/placebo treatment [b]		◆———	———	———	———◆
Trial intervention dispensed/collected		X [c]	X	X	X [d]
Relevant risk factors [e]		X	X	X	X
Systolic and diastolic BP		X	X	X	X
Weight		X	X	X	X
NYHA Functional Classification (I-IV)			X	X	X
CCS angina class (I-IV)			X	X	X
HbA_{1c} [f]		X	X	X	X
ECG		X	X	X	X
Efficacy outcomes [g]		X	X	X	X
Safety events [h]		X	X	X	X
Additional revascularization therapy (PCI/CABG)		X	X	X	X
ICD implantation			X	X	X
EQ-5D-5L/3L [i]		◆———	———	———	———◆

Trial schedule. [a]Minimum follow-up time = 3 months at last visit. [b]Patients randomized 1:1 to receive oral treatment with 10 mg dapagliflozin or placebo, once daily on top of standard of care. [c]Trial intervention dispensation only. [d]Trial intervention collection only. [e]Smoking, hypertension, dyslipidemia (defined as statin treatment). From Visit 2 and onwards only smoking and diabetes. [f]In the UK, it is optional to perform additional HbA_{1c} measurements at month 7 and 17 (±1 month). [g]Efficacy events, any potential heart failure hospitalization and all fatal events will be sent for adjudication to evaluate if fulfilling criteria for outcome event. In addition, MI and stroke outcomes as judged by the Investigator will be reported. [h]Serious adverse events (defined as adverse events that lead to hospitalization or death), will be collected from randomization. [i]EQ-5D-5L will be collected from Unify App users 3 days after discharge and then every month until patient's last visit, and data from the EQ-5D-3L questionnaire will be collected from all patients included in the Swedish SEPHIA (SEcondary Prevention after Heart Intensive care Admission) registry. *BP*, blood pressure; *CABG*, coronary artery bypass grafting; *CCS*, Canadian Cardiovascular Society; *ECG*, electrocardiogram; *EQ-5D-5L*, EuroQol five-dimensional five-level questionnaire; *HbA_{1c}*, glycated hemoglobin; *ICD*, implantable cardioverter defibrillator; *MI*, myocardial infarction; *NYHA*, New York Heart Association; *PCI*, percutaneous coronary intervention.

Data management

Patient data relating to the trial were collected by exporting data from SWEDEHEART or MINAP into the electronic data capture system (EDC). The investigator was responsible for verifying that data entries were accurate by an electronic signature in the EDC. A few trial-specific data that are not part of clinical routine were recorded manually, for example, date of consent and BP at randomization. In Sweden, most of the follow-up data from 6 to 10 weeks and 12 months post MI hospitalization were collected by exporting data from SWEDEHEART into the electronic Case Report Form (eCRF) system. The SWEDEHEART registry was used both for collection of blood sample results and the follow-up variables, which were included in the SEcondary Prevention after Heart Intensive care Admission (SEPHIA) registry. The follow-up in the UK replicated the follow-up routine in Sweden. However, the UK part of the trial required the implementation of trial-specific follow-up routines due to the lack of a specific follow-up component of the MINAP registry. Data capture from follow-up visits after 12 months was performed directly in the eCRF in both UK and Sweden. Vital status was collected by exports from the registries in both countries throughout the trial (for more information on the SWEDEHEART and MINAP registries, see Appendix A).

Trial monitors performed ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel were accurate, complete, and verifiable from source documents; that the safety and rights of participants were protected; and that the trial was conducted in accordance with the currently approved protocol and any other trial agreements, ICH-GCP, and all applicable regulatory requirements.

The statistical analyses will be performed by Uppsala Clinical Research Center, Sweden, and the Sponsor, AstraZeneca.

Data monitoring committee

An independent Data Monitoring Committee (DMC) was appointed jointly by the Sponsor and the academic leadership of the trial. The DMC was responsible for safeguarding the interests of the patients in the outcome trial by assessing the safety of the intervention during the

Table 1. DAPA-MI inclusion/exclusion criteria

Inclusion criteria

1. Men or women age ≥18 at the time of signing the informed consent
2. Confirmed MI, either STEMI or NSTEMI, according to the fourth universal definition of MI,[38] within the preceding 7 days, or 10 days if earlier randomization is not feasible
3. Imaging evidence of impaired regional or global LV systolic function at any timepoint during the index MI-related hospitalization (established with echocardiogram, radionuclide ventriculogram, contrast angiography or cardiac MRI) OR definitive evidence on ECG of a Q-wave MI (defined as presence of Q waves in two or more contiguous leads, excluding leads III and aVR, and meeting all the following criteria: at least 1.5 mm in depth; at least 30 ms in duration; and, if R wave present, more than 25% of the size of the subsequent R wave)
4. Hemodynamically stable at randomization (no episodes of symptomatic hypotension, or arrhythmia with hemodynamic compromise in the last 24 hours)
5. Capable of giving signed informed consent that includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in the protocol
6. Provision of signed and dated, written informed consent prior to any mandatory trial specific procedures, sampling, and analyses

Exclusion criteria

1. Known type 1 diabetes mellitus (T1DM) or T2DM at the time of admission. Patients with hyperglycemia, but without a diagnosis of diabetes mellitus prior to the index event, were eligible at the discretion of the investigator
2. Chronic symptomatic HF with a prior HHF within the last year and known reduced ejection fraction (LVEF≤40 %), documented before the current MI hospitalization
3. Severe chronic kidney disease (eGFR <20 mL/min/1.73 m^2 by local laboratory), unstable or rapidly progressing kidney disease at the time of recruitment
4. Severe hepatic impairment (Child-Pugh class C) at the time of recruitment for the trial
5. Active malignancy requiring treatment at the time of screening, except for basal cell- or squamous cell carcinoma of the skin, presumed possible to treat successfully
6. Any non-CV condition, eg, malignancy, with a life expectancy of less than two years based on the investigatorś clinical judgment
7. Currently on treatment, or with an indication for treatment, with a sodium glucose co-transporter 2 inhibitor (SGLT2-inhibitor)
8. Known intolerance to dapagliflozin
9. Participation in
    a) another trial with a non-approved investigational drug or blinded treatment with a CV or glucose-lowering medication
    b) the planning and/or conduct of the trial (applies to AZ staff, UCR staff, and/or staff at the trial site)
    c) previous randomization in the present trial
10. Judgment by the investigator that the participant should not participate in the trial if the participant is unlikely to comply with trial procedures, restrictions and requirements, or any condition in the opinion of the Investigator that would make participation unsafe or unsuitable
11. Women of childbearing potential (ie, those who are not chemically or surgically sterilized or postmenopausal):
    a) Who are not willing to use a highly effective method of contraception, OR
    b) Who have a positive pregnancy test, OR
    c) Who are breast-feeding

trial, and for reviewing the overall conduct of the trial. An independent statistical group had access to the individual treatment codes and was able to merge these with the collected trial data and provide them to the DMC during the trial.

Clinical endpoint committee

An independent, blinded Clinical Endpoint Committee (CEC) was appointed jointly by the Sponsors and the academic leadership of the study to adjudicate HHF and CV death events. Investigators reported potential events via eCRFs in real time. Once a potential event had been identified, a complete package of information was collected and sent to the CEC within 2 weeks of identification. The CEC reviewers set a target to evaluate the complete package within 4 weeks of receipt.

Trial objectives and outcomes

The composite of CV death and HHF was initially chosen as the primary outcome for the DAPA-MI trial. However, during the course of the trial, it became evident that the number of collected primary composite outcomes was substantially lower than anticipated. Thus, in February 2023, the trial was modified from an event-driven time-to-event approach, based on number of collected HHF and CV death events, to a hierarchical composite outcome approach including clinically-relevant cardiometabolic outcomes. The description of the trial herein is based on the amended protocol.

The revised primary trial objective is to determine the effect of dapagliflozin 10 mg QD vs placebo, when added to SoC, by using the win-ratio method to compare the hierarchical composite outcome of (ordered according to descending clinical importance):

1. Death (first CV death, followed by non-CV death)
2. HHF (first adjudicated, followed by investigator-reported)
3. Non-fatal MI (investigator-reported)

Table 2. Outcomes

Primary composite outcome

The hierarchical composite outcome of:

1. Death (first CV death, followed by non-CV death)
2. Hospitalization due to heart failure (first adjudicated, followed by investigator reported)
3. Non-fatal MI
4. AF/flutter event
5. New onset of T2DM
6. NYHA Functional Classification at last visit
7. Body weight decrease of at least 5% at last visit

Secondary outcomes

- The hierarchical composite outcome of:
  1. Death (first CV death, followed by non-CV death)
  2. Hospitalization due to heart failure (first adjudicated, followed by investigator reported)
  3. Non-fatal MI
  4. AF/flutter event
  5. New onset of T2DM
  6. NYHA Functional Classification at last visit
- Time to the first occurrence of any of the components of this composite:
  - HHF
  - CV death
- Time to the first occurrence of any of the components of this composite:
  - CV death
  - HHF
  - MI
- Time to the first occurrence of any of the components of major adverse cardiovascular events (MACE):
  - MI
  - Stroke (incl. ischemic, hemorrhagic, and undetermined stroke)
  - CV death
- Time to CV death
- Time to the first occurrence of a fatal or a non-fatal MI
- Time to new onset of T2DM
- Change from baseline in body weight
- Time to hospitalization for any cause
- Time to death of any cause

Safety outcome

Adverse events defined as events that lead to:

- death; or
- hospitalization

4. Atrial fibrillation (AF)/flutter event (serious adverse event (SAE) leading to hospitalization regardless of medical history at baseline)
5. New onset of T2DM (investigator-reported)
6. NYHA Functional Classification at last visit. Class IV < class III < class II < class 0/I
7. Body weight decrease of $\geq$ 5% at last visit

The key secondary outcome will consist of the same composite as the primary outcome, excluding body weight reduction (see Table 2 for prespecified secondary outcomes).

Potential outcome events were identified through (1) questioning the patient about their overall health and symptoms; and (2) information received through standard medical practice, including findings on physical examination, medical imaging, and laboratory data.

All potential HHF outcomes were recorded in the eCRF and submitted to the CEC for adjudication. Similarly, the CEC members adjudicated and classified all deaths as CV, non-CV, or undetermined cause of death. The outcomes of MI and stroke relied on investigator reporting and were not adjudicated centrally. The rationale for this was that diagnoses of MI and stroke are well-defined in broadly accepted guidelines and by objective routine diagnostic procedures (ECG and cardiac troponin levels to diagnose MI, and brain imaging to support stroke diagnosis). (For further information on outcome definitions, see Appendix B.)

New onset T2DM was reported by the investigator in a dedicated eCRF form and confirmed for trial purposes by: (1) incident T2DM diagnosis necessitating initiation of treatment with a glucose-lowering medication; OR (2) $HbA_{1c} \geq 6.5\%$ (48 mmol/mol) measured by the local

laboratory at two consecutive time points. For patients who developed a new labeled indication for SGLT2 inhibition in the opinion of the investigator, discontinuation of the trial medication was recommended and SGLT2 inhibitor treatment was started at the discretion of the investigator. Immediate discontinuation of the investigational treatment was recommended for patients who presented with signs and symptoms consistent with ketoacidosis.

For change in body weight, only repeat measurements after the index hospitalization will be considered. Last visit is defined as the last visit with body weight measurement available, within each pair-wise comparison. Repeated measures analyses will be used for change from baseline to each relevant time point.

The maximum follow-up during the DAPA-MI trial was 2.5 years, with an expected average of 6-month follow-up. The majority of adverse events are anticipated to occur in the first 6 months following MI and a significant effect of SGLT2 inhibition treatment can be observed during this time. For example, patients in the EMMY trial with a mean baseline left ventricular ejection fraction of approximately 50% showed a significantly greater left verntricular improvement after treatment with empagliflozin 10 mg daily compared with placebo within 6 months.[12] Therefore, an early treatment effect is anticipated also in patients with mildly reduced LV function.

Safety assessments

The number and type of adverse events leading to death or hospitalization will be compared to assess the safety of treatment with 10 mg dapagliflozin. To comply with national legislation regarding risk assessment, all SAEs (defined as an event that results in death; is immediately life threatening; requires in-participant hospitalization or prolongation of existing hospitalization; causes persistent or significant disability or incapacity; results in congenital anomalies or birth defects; or is an important medical event that may jeopardize the participant or may require medical treatment to prevent one of the outcomes listed above) were collected for patients enrolled in the UK. Fatal events during the trial were recorded by the investigator, supported through regular registry checks. Deaths in both Sweden and the UK are routinely captured by their respective population registries and automatically added to SWEDEHEART and requested for linkage with the MINAP data, respectively.

Statistical analyses

The primary hierarchical composite outcome is ordered according to clinical importance: death, HHF, nonfatal MI, AF/flutter, new onset of T2DM, symptoms of HF as assessed by NYHA Functional Classification (class IV $<$ class III $<$ class II $<$ class 0/I) at last visit, and body weight loss $\geq$ 5% at last visit. The primary outcome will be assessed using the win-ratio method and each patient in the treatment group will be compared with each patient in the control group to determine the win/loss/tie within each pair across each of the multiple outcomes. For each pair-wise comparison, only events occurring within the shared follow-up time will be considered, that is, the minimum follow-up time within each pair, resulting in censoring at the shared follow-up time for the patient with the longest follow-up time as it is unknown what would happen to the patient with shorter follow-up time after that timepoint.

The key secondary outcome will be analyzed using the win-ratio method in a similar manner as the primary outcome, but excluding the body weight component. All secondary time-to-event outcomes will be compared using a Cox proportional hazards model with a factor for treatment group, stratified by country. The secondary outcome of change in body weight will be analyzed with a repeated measure analysis using a mixed model. The model will present least squares (LS) mean estimates and 2-sided 95% confidence intervals (CIs) for treatment difference as well as change from baseline within treatments.

The analysis set for the primary and all secondary efficacy outcomes is the intention-to-treat (ITT) population, consisting of all patients who have been randomized to the trial treatment, irrespective of their protocol adherence and continued participation in the trial.

For the safety analysis set, all randomized patients who received at least one dose of trial treatment will be included. The number and percent of patients with adverse events leading to hospitalization or death and all SAEs, will be summarized by treatment group. For safety analyses, summaries will be provided using both on-treatment observations and all observations, regardless of whether patients are on or off trial treatment.

Sample size estimates

The primary objective of the trial is to determine the clinical effect of dapagliflozin vs placebo. The objective will be assessed with a hierarchical composite outcome and analyzed using the win-ratio method.[15] Assuming a true win-ratio of 1.20 between dapagliflozin and placebo, 4,000 patients will provide a statistical power of 80%, based on simulations, for the test of the primary composite outcome, using a 2-sided alpha of 5%. This is based on an overall 1:1 allocation between dapagliflozin and placebo. The assumed win-ratio of 1.20 is considered clinically relevant.[16]

Discussion

Survivors of MI remain at substantial risk for subsequent adverse CV events,[17] including risk for developing HF and death.[18,19] HF is one of the leading causes of all hospital admissions, substantially contributing to costs and resource utilization for healthcare systems.[20,21] The

currently available therapeutic strategies to reduce the risk for development of HF following MI were all introduced more than a decade ago and include early reperfusion therapy for STEMI, early initiation and proper dose-titration of ACE inhibitors/angiotensin II receptor blockers and mineralocorticoid-receptor antagonists, routine use of intense-dose statin therapy, and careful evaluation and re-evaluation of indications for beta-blocker therapy during and after the MI hospitalization.[22,23] Despite these advancements, patients surviving an acute MI event remain at high CV risk, including at high risk for developing HF.[17,18] Therefore, the DAPA-MI trial was designed to address such an unmet need for a new effective therapy for patients surviving MI that could be added to the current guideline-supported therapies to reduce HF risk.

The hypothesis is that treatment with dapagliflozin 10 mg will reduce death, HHF, and other adverse HF and cardiometabolic outcomes in patients with a recent MI and without T2DM.

The trial design of DAPA-MI uses an R-RCT framework, a trial concept that has been used in many prior trials,[24,25] but not previously used in trials aiming for regulatory application for new product labeling or indication. By allowing collection of patient data and outcomes from clinical registries already incorporated into routine health care practice, the R-RCT framework ensures a robust yet streamlined trial capable of producing high-quality evidence of clinical effectiveness and safety. As most health quality registries mainly collect data regarding disease management, a common limitation of pragmatic trials is the lack of outcome data.[26] In the case of DAPA-MI, this was handled through routine import of patient data such as all-cause death from other health registries to the EDC system. Multinational R-RCTs also face the problem of differences in condition-specific standards of care and processes of care, which lead to differences in registry variables and the timepoints of data collection. For example, in Sweden, following an MI, patients have a dedicated secondary prevention visit at 6 to 10 weeks postdischarge as well as a 12-month follow-up visit. In the UK, there is heterogeneity between sites in terms of follow-up arrangements. For the purpose of this trial and to align the collected data from the two countries, follow-up visits in the UK were instead scheduled at 6 to10 weeks post discharge and further arrangements were made to implement the follow-up visit at 12 months.

The R-RCT model, together with remote surveillance using the CleverCap Lite technology and the Unify mobile software application, has reduced the burden on the health care system during the trial and enabled fast recruitment of patients and efficient data collection.

The DAPA-MI trial was initially designed with the primary composite outcome of time to first CV death or HHF. However, significant improvements in the treatment of patients with MI during recent years, largely due to an improved quality of care, have substantially reduced the incidence of post-MI adverse outcomes such that trial designs and analysis methods had to be modified in order to ensure adequate statistical power using modified trial primary outcomes and alternative analytics.[1,27] Therefore, instead of performing an event-driven trial that would only take the first event of HHF and CV death events into account, after the observance of a particularly low incidence of primary outcome events among enrolled patients over several iterative analyses of the pooled trial data, it was decided by the academic steering committee to change the DAPA-MI primary analysis to a hierarchical composite outcome that would include a composite of clinically-relevant cardiometabolic outcomes ranked by perceived clinical importance using win-ratio methods for analysis. This would allow for a comprehensive trial of the CV benefits of dapagliflozin treatment in patients with a recent MI, especially considering the high-quality SoC already available to these patients. Therefore, the original composite primary outcome was amended with addition of all-cause mortality, MI, AF/flutter events, new onset of T2DM, NYHA Functional Classification at last visit, and a body weight decrease of $\geq$5% at last visit. Accordingly, in February 2023, the sample size was re-calculated and reduced from about 6,400 to approximately 4,000 patients.

Each of the components added to the composite primary outcome evaluates the beneficial effect of dapagliflozin on a series of cardiometabolic outcomes important for a patient who has recently suffered an MI. The DECLARE-TIMI 58 trial showed that treatment with 10 mg dapagliflozin reduced the risk of a first AF/flutter event by 19% and the total number of events by 23% in patients with T2DM with or without previous history of AF, atherosclerotic CV disease, or HF.[28] AF or flutter are common in patients with T2DM and the combination of the two diseases leads to high risk of CV complications.[29,30] The DAPA-HF and DAPA-CKD trials also showed a reduction in new onset of T2DM in patients treated with 10 mg dapagliflozin,[31] together with the previously mentioned reduction in HHF and CV death.[7,32] Prevention of both AF/flutter and T2DM could thus lead to substantial long-term health benefits for patients with MI.

Dapagliflozin treatment does not only result in decreased HHF but also leads to significant, early, and sustained improvements in NYHA class in patients with or without T2DM.[33] Patients in the DELIVER trial showed marked improvement in NYHA classification together with improved patient-reported health status and KCCQ (Kansas City Cardiomyopathy Questionnaire) clinical and overall summary scores after treatment with dapagliflozin.[33] NYHA classification can be used to predict future HF events, but is also an indicator of all-cause mortality in patients with HF, emphasizing the importance

of functional classification in assessment of subsequent events in MI patients.[34]

Body weight reduction was added as the last outcome in the hierarchical composite endpoint due to the clinical benefit of weight loss in individuals with overweight/obesity at risk for CV disease.[35] According to the ACC/AHA guidelines (2019), a clinically meaningful weight loss (≥5% initial weight) is associated with moderate improvement in BP, low-density lipoprotein cholesterol (LDL-C), triglyceride, and glucose levels.[36] ESC guidelines (2017) also recommend maintaining a healthy weight or losing weight for patients who recently experienced an MI.[22] Previous trials have shown a significant impact of dapagliflozin 10 mg on weight loss.[5,7,32,37] A study specifically designed to determine the underlying components of this weight loss showed that the change in body mass was predominantly due to a reduction in abdominal visceral and subcutaneous adipose tissue.[37] Thus, including a body weight decrease of ≥5% at last visit to the primary composite endpoint was considered highly relevant when comparing the two treatment groups.

In summary, the revised outcome variables in the hierarchical analysis provide a comprehensive picture of the clinical benefits of dapagliflozin treatment in patients with a recent MI.

A similar trial on the SGLT2-inhibitor empaglifozin, a streamlined, multicenter, randomized, parallel group, double-blind placebo-controlled superiority trial to evaluate the effect of EMPAgliflozin on hospitalization for heart failure and mortality in patients With aCuTe Myocardial Infarction (EMPACT-MI), is ongoing and its results will likely complement those of the DAPA-MI trial. The trial is designed to enroll 6,522 patients with MI and high risk for HF (including patients with history of diabetes mellitus) and will analyze time to first HHF or all-cause mortality as the primary outcome (ClinicalTrials.gov Identifier: NCT04509674).

Trial status

Patient enrolment started in December 2020 and recruitment of 4,017 patients was completed on March 8, 2023. Trial completion is estimated to Q3, 2023. Protocol version 4.0, February 23, 2023.

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Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary material

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