Heart Failure with Reduced Ejection Fraction Polypill in Sri Lanka: A Multi-Center Type I Hybrid Randomized Controlled Trial

Statistical Analysis Plan

ClinicalTrials.gov Identifier: NCT07569640
Sri Lanka Clinical Trials Registry SLCTR/2026/017
WashU IRB Protocol #: 202605087

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Administrative Information

1. Title, Trial Registration, and IRB

Title: Heart Failure with Reduced Ejection Fraction Polypill in Sri Lanka: A Multi-Center Type I Hybrid Randomized Controlled Trial

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2. Version Number, Protocol Number, Change Summary

Date	Protocol version no.	SAP version no.	Summary of changes
4 August 2026	4.0	1.0	Initial version; SAP finalized prior to database lock.

3. Roles and Responsibilities

Names, affiliations, and roles of SAP contributors:

Charles W. Goss: Assistant Professor of Biostatistics at the Institute for Informatics, Data Science, and Biostatistics, Washington University School of Medicine: *Co-Investigator and lead statistician*

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Introduction

4. Background and Rationale

This Statistical Analysis Plan (SAP) describes the planned statistical analyses for the "Heart Failure with Reduced Ejection Fraction Polypill in Sri Lanka: A Multi-Center Type I Hybrid Randomized Controlled Trial." This trial evaluates a fixed-dose combination HFrEF polypill compared with usual care in adults with HFrEF in Sri Lanka. This trial is funded by extramural support from the National Institutes of Health (R00HL157687, PI: Anubha Agarwal) and intramural funds from Washington University in St. Louis. Washington University in St. Louis serves as the trial sponsor and assumes overall sponsor responsibilities, including trial oversight and coordination. The funding agencies have no role in the design or conduct of the trial; data collection, analysis, or interpretation; or the decision to submit results for publication.

This SAP was developed and finalized prior to database lock and finalization of the study dataset. All analyses specified herein are considered pre-specified. Any deviations from this plan will be documented with scientific justification.

5. Objectives

Aim 1: The primary efficacy aim is to evaluate whether a HFrEF polypill reduces the composite rate of cardiovascular disease mortality and recurrent heart failure hospitalizations compared with usual care in adults with HFrEF in Sri Lanka over a minimum of 12 months of follow-up using a multi-center, type I hybrid, randomized controlled trial design.

Hypothesis 1: We hypothesize that the HFrEF polypill will reduce the rate of the composite outcome compared with usual care. The null hypothesis states that the rate ratio equals 1.0, indicating no difference between treatment groups, while the alternative hypothesis states that the rate ratio differs from 1.0.

Secondary and safety analyses will also be evaluated. Secondary efficacy outcomes include the individual components of the primary outcome (cardiovascular disease mortality and recurrent heart failure hospitalizations), all-cause mortality, and changes from baseline to 12 months and end of study in left ventricular ejection fraction, BNP levels, health-related quality of life assessed by the Kansas City Cardiomyopathy Questionnaire, and New York Heart Association functional class. Additionally, we will assess medication adherence using pill counts and the MARS-5 questionnaire, persistence defined as continuation of assigned therapy, and dose optimization defined as the proportion achieving target doses (Strength 3 of the polypill, or comparable individual GDMT doses in the comparator arm).

Safety outcomes include the proportion of participants experiencing serious adverse events according to Good Clinical Practice guidelines, adverse events of special interest (symptomatic hypotension, diabetic ketoacidosis, severe hypoglycemia, lower limb amputation, falls, hyperkalemia, and worsening renal function), and adverse events leading to drug discontinuation. We will also evaluate mean changes from baseline in continuous serum potassium and serum creatinine at 12 months and end of study, controlling for baseline values.

Hypothesis 2 (superiority): The HFrEF polypill will improve secondary efficacy and safety outcomes, including individual components of the primary composite, all-cause mortality, left ventricular ejection fraction, BNP, health-related quality of life, and NYHA functional class, medication adherence, and safety outcomes compared with usual care.

Study Methods

6. Trial Design

Multi-center, parallel group, open-label, type I hybrid randomized controlled trial.

7. Randomization

Participants will be randomized in a 1:1 ratio to receive either the HFrEF polypill (intervention arm) or usual care (comparator arm). Randomization will be performed centrally using the REDCap randomization module with a computer-generated random allocation sequence. Randomization will be stratified by study site and sex

using variable block sizes to maintain allocation concealment.

8. Sample Size

The target sample size is 1,672 participants (836 per arm), calculated using the Lin-Wei-Yang-Ying (LWYY) method for recurrent event analysis, which accounts for within-subject correlation of events and heterogeneity in recurrence rates. The calculation assumes a control arm annual event rate of 30% for the composite of cardiovascular death and recurrent heart failure hospitalizations. The expected treatment effect corresponds to a rate ratio of 0.71 (29% relative risk reduction). Using a two-sided significance level of $\alpha = 0.05$ and targeting 80% power, the base calculation yields 1,505 participants after incorporating a dispersion factor ($\varphi = 1.4$). Inflating by 10% for loss to follow-up (i.e., dividing by 0.90, so that approximately 1,505 evaluable participants remain after 10% attrition) yields 1,672 participants.

9. Framework of Primary Hypotheses

The HFrEF polypill will reduce the rate of the composite outcome (cardiovascular disease mortality and recurrent heart failure hospitalizations) compared with usual care, demonstrating superiority. The null hypothesis states that the rate ratio equals 1.0, indicating no difference between treatment groups. The alternative hypothesis states that the rate ratio differs from 1.0 The hypothesis will be tested two-sided at $\alpha = 0.05$ and superiority of the polypill is concluded if the rate ratio is significantly less than 1.0.

Primary estimand (ICH E9 R1). The primary estimand targets the population-averaged treatment effect of initiating the HFrEF polypill regimen:

- Population: all randomized participants — adults with HFrEF meeting the eligibility criteria.
- Treatment conditions: HFrEF polypill-based care versus usual care, as randomized.
- Endpoint: number of composite events (cardiovascular death and recurrent heart failure hospitalizations) from randomization to the common study end date.
- Intercurrent events: non-adherence to or discontinuation of the polypill, and initiation of open-label GDMT in either arm, are handled by a treatment-policy strategy — all events are counted as randomized. Non-cardiovascular death is handled by censoring follow-up at the date of non-cardiovascular death. Cardiovascular death is not an intercurrent event; it is a counted component of the endpoint.
- Population-level summary: the rate ratio between arms, estimated by the LWYY marginal proportional-rates model.

GDMT uptake by class will be summarized by arm over time to characterize contamination.

10. Statistical Interim Analysis and Stopping Guidance

The Data Safety and Monitoring Plan (DSMP) documents the provisions to monitor the data and ensure safety of all study participants. The DSMB will review unblinded descriptive data at approximately the mid-point of the trial in a closed session and will have authority to recommend early termination of the trial for any concerns. The DSMB may also convene ad hoc meetings if suspected unexpected serious adverse reactions or other urgent safety concerns arise. Decisions regarding early termination for futility or safety will be based on observed treatment effects, safety signals, event accrual, and overall study conduct. The DSMB will provide recommendations to the study team regarding continuation, modification, or termination of the trial. The mid-point DSMB review is descriptive only and does not include a formal efficacy hypothesis test; accordingly, no alpha is spent at the interim analysis, and the final analysis is conducted at the full two-sided significance level of $\alpha = 0.05$

11. Timing of Final Analysis

Stage 1: DSMB safety review at approximately mid-point of trial
Stage 2: Final analysis after minimum 12 months' follow-up for all participants

12. Timing of Outcome Assessments

Visit	Screening (V1)	Randomization (V2)	1 Month (V3)	3 Month (V4)	6 Month (V5)	9 Month (V6)	Month 12 (V7)	Every 3 months until study end (V8 +)	EOS
Day	**Day -15 to 1**	**Day 1**	**Day 28 ± 7**	**Day 90 ± 14**	**Day 180 ± 14**	**Day 270 ± 14**	**Day 360 ± 14**	**After Day 360, Every 90 ± 14 days**	**EOS**
Informed consent	X								
Eligibility assessment	X	X							
Demographics and medical history	X								
Vital signs (BP, HR, weight)	X		X	X	X	X	X		X
Labs: Serum potassium	X		X	X	X	X	X		X
Labs: Serum creatinine	X		X	X	X	X	X		X
Labs: eGFR	X		X[a]	X[a]	X[a]	X[a]	X[a]		
Labs: Serum sodium	X		X	X	X	X	X		X
Labs: BNP	X						X		X
Labs: Pregnancy test for women of childbearing potential	X		X[b]	X[b]	X[b]	X[b]	X[b]		
ECG/Interpret ECG	X								
Transthoracic echocardiogram (LVEF assessment)[c]	X						X		X
Randomization		X							
Dispense study drug (HFrEF polypills)		X	X	X	X	X	X	X	
HFrEF polypill titration decision (per protocol)			X	X	X	X	X		
GDMT reconciliation and pill count of HFrEF polypill or individual GDMT		X	X		X		X		X
Assessment of discontinuation of HFrEF polypill or individual GDMT			X	X	X	X	X		
Assessment of CVD mortality			X	X	X	X	X	X	X
Assessment of HF hospitalizations			X	X	X	X	X	X	X
Assessment of all-cause mortality			X	X	X	X	X	X	X
KCCQ	X						X		X
NYHA functional class	X						X		X
Assessment of adverse events/AESI/SAE			X	X	X	X	X	X	X
MARS-5 adherence questionnaire	X		X		X		X		X
Concomitant medications	X	X	X	X	X	X	X		X
Confirm contact information for study retention	X	X	X	X	X	X	X	X	

a- eGFR results required at screening. At follow-up, to be recorded if available only.
b- Urine pregnancy test done at screening. If determined required by the investigator, will be done at follow-up as well.
c- Echo reports within 6 months of screening can be considered.

AE: Adverse Event; BP: Blood Pressure; CVD: Cardiovascular Disease; ECG: Electrocardiogram; GCP: Good Clinical Practice; GDMT: Guideline-Directed Medical Therapy; HF: Heart Failure; HFrEF: Heart Failure with Reduced Ejection Fraction; HR: Heart Rate; KCCQ-23: Kansas City Cardiomyopathy Questionnaire (23-item); LVEF: Left Ventricular Ejection Fraction; MARS-5: Medication Adherence Report Scale (5-item); BNP: B-type Natriuretic Peptide; NYHA: New York Heart Association

Statistical Principles

13. Confidence intervals and P values

All statistical tests will be two-sided with a significance level of α = 0.05 unless otherwise specified. Confidence intervals will be reported at the 95% level. Continuous variables will be summarized using means and standard deviations or medians and interquartile ranges as appropriate. Categorical variables will be summarized using frequencies and percentages. Because the trial has a single primary outcome, no multiplicity adjustment will be applied. Secondary and safety outcomes are regarded as supportive and will be summarized with 95% confidence intervals without formal multiplicity control and interpreted accordingly.

14. Adherence and protocol deviations

Adherence to the study protocol will be monitored throughout the trial. Protocol deviations will be documented, categorized by type and severity, and reported to the DSMB. Major protocol deviations that may impact participant safety or data integrity will be evaluated for their potential effect on study outcomes and the per-protocol analysis population.

15. Analysis populations

The primary analysis will be conducted on the intention-to-treat (ITT) population. Sensitivity analyses will be conducted in the modified ITT, per protocol, and complete case populations.

Intention to Treat (ITT): Defined as all participants analyzed according to the group they were randomized to, regardless of adherence.

Modified ITT: All randomized participants who receive at least one dose of the HFrEF polypill (intervention arm) or, in the usual-care arm, complete at least one post-randomization study assessment (comparator arm).

Per Protocol: Participants who complete the study without major protocol violations.

Complete Case: Participants with complete outcome data for the analyzed outcome

Trial Population

16. Eligibility

Inclusion Criteria:

1. Adults (≥18 years old)
2. Diagnosis of heart failure with reduced ejection fraction (HFrEF) including
    a) clinical symptoms or clinical signs or natriuretic peptide elevation AND
    b) echocardiographic or other evidence of reduced left ventricular ejection fraction (EF ≤40%)
3. New York Heart Association Class II, III, or IV symptoms

Exclusion Criteria:

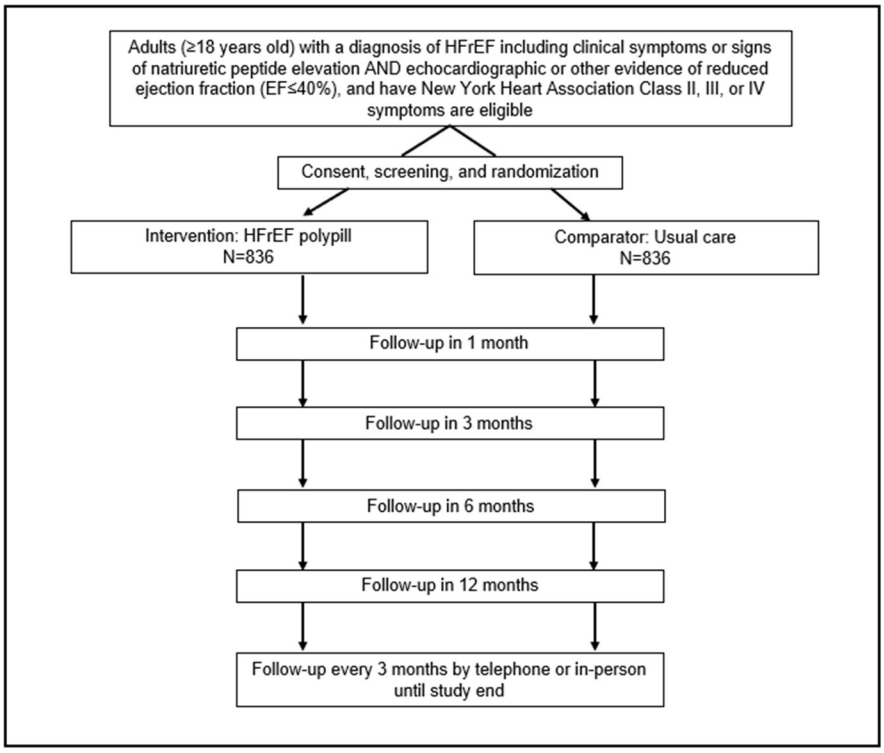
1. Known contraindication to any of the HFrEF polypill components (e.g., advanced renal disease, bradycardia, allergy, amongst others).
2. Significant renal impairment (estimated glomerular filtration rate <30 mL/min/1.73 m2)
3. Raised serum potassium >5 mEq/L.
4. Symptomatic hypotension or systolic BP <100 mmHg as per the average of last 2 of the 3 measurements at visit 1.
5. Symptomatic bradycardia or second or third-degree heart block without a pacemaker on ECG review at visit 1.
6. History of type 1 diabetes mellitus.
7. Women who are pregnant, breastfeeding or of childbearing potential and are not using and do not plan to continue using a highly acceptable form of contraception throughout the study (pharmacological or barrier methods).
8. Concomitant illness, physical impairment, or mental condition which in the opinion of the study team/ primary physician could interfere with the conduct of the study including outcome assessment.
9. Participation in a concurrent interventional medical investigation or pharmacologic clinical trial. Patients in observational, natural history or epidemiological studies not involving an intervention are eligible.
10. Participant's responsible physician believes it is not appropriate for participant to participate in the study.

11. Inability or unwillingness to provide written informed consent.
12. Involvement in the planning and/or conduct of the study.
13. Unable to complete study procedures and/or plan to move out of the study site area in the next 12 months.

This study will not recruit participants from a vulnerable population, including a) individuals who are not yet adults (minors): i.e., infants, children, or teenagers or b) prisoners or other detained individuals.

17. Recruitment

We will identify patients during hospitalization or routine clinic visits and from a list of potentially eligible participants at each participating site. The study staff will review these potential participants' charts and ensure permission from the patients' treating physician, if necessary, to contact for potential participation in the study. If patients express interest (either during contact when hospitalized, in outpatient clinic, or by telephone), then the screening visit will be scheduled (either during hospitalization immediately prior to discharge, during outpatient clinic, or a separate clinic appointment). During the screening visit, the study team will obtain informed consent and conduct baseline assessments to determine eligibility status. Eligible participants will be randomized.



18. Withdrawal/follow-up
Participants may withdraw consent for treatment, for data collection, or both. The reason for withdrawal will be documented. Participants who withdraw consent only from intervention treatment will continue to be followed for outcomes according to the study schedule. Participants who withdraw consent for data collection will be censored at the time of withdrawal. Every effort will be made to minimize loss to follow-up, including attempts to contact participants via telephone and alternative contact persons. Vital status will be ascertained through national registries when available and with participant consent. Participants lost to follow-up will be censored at their last known contact date in time-to-event analyses.

19. Screening data
Descriptive data will determine whether the enrolled sample differs from the screened but not enrolled sample on the following variables:

- Age
- Sex
- NYHA class
- Left ventricular ejection fraction
- Baseline medications

20. Baseline patient characteristics
Descriptive statistics (means and standard deviations, medians and interquartile ranges, or frequencies) will be generated for the following variables in the enrolled and randomized sample. Consistent with CONSORT guidelines, baseline characteristics will be presented descriptively without statistical hypothesis testing.:

- Age
- Sex
- Clinic/site
- Socioeconomic position (education, employment, household income)
- Marital status
- Number of people in household
- BMI (height and weight)
- Baseline heart rate and blood pressure
- Baseline NYHA class, time since HFrEF diagnosis, and etiology
- Baseline cardiovascular medications
- Baseline comorbidities (diabetes, cancer, asthma, sleep apnea, CKD, COPD, mental health disorders)
- Baseline elevated cholesterol
- Baseline cardiovascular disease history (hypertension, ischemic heart disease, stroke, heart failure)

21. Outcome Definitions
Primary Analysis: Composite rate of cardiovascular disease mortality and recurrent heart failure hospitalizations over study duration
Cardiovascular disease mortality is defined as death due to acute myocardial infarction, worsening heart failure, stroke, sudden cardiac death, arrhythmia, pulmonary embolism, cardiovascular procedures or their complications, other vascular causes, or any death of unknown cause unless a non-cardiovascular etiology is clearly established.

HF hospitalization is defined as any unplanned hospitalization for at least 24 hours, for which the primary cause is heart failure, accompanied by objective evidence of decompensation and requiring initiation or intensification of HF-specific therapy, occurring after a documented period of clinical stability of at least 12 hours since the prior HF event.

Assessed throughout the study and specifically at 1-month, 3-month, 6-month, 9-month, and 12-month study visits and thereafter, every 3 months by telephone or in-person until study end using structured questionnaires.

Adjudicated by the blinded Outcome Adjudication Committee.

Secondary outcomes:

1. Rate of cardiovascular disease mortality over study duration
2. Rate of recurrent heart failure hospitalizations over study duration
3. Rate of all-cause mortality over the study duration
4. Change in left ventricular ejection fraction at 12-months and end of study assessed by transthoracic echocardiogram
5. Change in BNP levels at 12 months and end of study
6. Change in overall and domain specific health-related quality of life at 12-months and end of study assessed by a translated validated version of the Kansas City Cardiomyopathy Questionnaire (KCCQ-23)
7. Change in physician-reported New York Heart Association class at 12-months and end of study
8. Adherence to guideline-directed medical therapy assessed by pill count and MARS-5 questionnaire at baseline, 1-, 6-, 12-months, and end of study. Persistence assessed as continuation of assigned therapy at each follow-up visit. Dose optimization assessed as proportion achieving target doses (Strength 3 of the polypill, or comparable individual GDMT doses in the comparator arm) at 6-, 12-months, and end of study.

Safety outcomes:

1. Proportion of participants with serious adverse events according to Good Clinical Practice guidelines over study duration
2. Proportion with adverse events of special interest (symptomatic hypotension, diabetic ketoacidosis, severe hypoglycemia, lower limb amputation, falls, hyperkalemia, and worsening renal function), each defined as in the protocol
3. Proportion of participants with adverse events leading to HF drug discontinuation over study duration
4. Mean change from baseline to 12-months and end of study in serum potassium (mEq/L)
5. Mean change from baseline to 12-months and end of study in serum creatinine (mg/dL)

22. Analysis Methods

Preliminary Analyses

For all analyses, in addition to the assessment of the distributional properties of key measures at follow-up, we will evaluate the nature and pattern of missing data. Baseline characteristics will be summarized by randomized arm using means and standard deviations or medians and interquartile ranges for continuous variables and counts and percentages for categorical variables, without significance testing. Follow-up time, person-time at risk, and the number of participants contributing to each analysis will be reported by arm. Unless otherwise specified, all efficacy and safety regression models will adjust for the randomization stratification variables (site and sex) and the pre-specified baseline covariates (age and baseline systolic blood pressure), in addition to the baseline value of the outcome where applicable.

Primary Analysis

The primary outcome will be analyzed using the Lin-Wei-Yang-Ying (LWYY) marginal proportional-rates model for recurrent events, fitted as an Andersen-Gill counting-process model with a robust sandwich variance estimator to account for within-subject correlation. Each participant contributes events and person-time from randomization until the earliest of cardiovascular death, withdrawal of consent, loss to follow-up, or the common study end date. Cardiovascular death is counted as an event within the composite counting process and terminates subsequent follow-up; non-cardiovascular death, withdrawal, and loss to follow-up are treated as censoring. The model estimates the rate ratio comparing HFrEF polypill-based care to usual care.

The model will be adjusted for the randomization stratification variables (site and sex) and pre-specified baseline covariates (age, baseline SBP). As a pre-specified sensitivity analysis, the composite will be re-analyzed using the Mao-Lin semiparametric proportional means model for the for composite recurrent-plus-terminal events, which accounts for the terminal event explicitly; agreement between the LWYY and Mao-Lin estimates will be reported. Cardiovascular death is additionally analyzed as a standalone secondary outcome.

Secondary outcomes will be analyzed using methods appropriate to each outcome type.

Cardiovascular and all-cause mortality will be analyzed using Cox proportional hazards regression, with Kaplan-Meier estimates, log-rank tests, and assessment of the proportional-hazards assumption. Recurrent heart failure hospitalizations will be analyzed using the Ghosh-Lin marginal mean-frequency model, which accounts for death as a competing risk, with the LWYY rate model reported as a supporting analysis. Because death is not a counted event in this endpoint, the Ghosh-Lin model is used to avoid bias from informative censoring by mortality. Time to first heart failure hospitalization will be analyzed using Cox proportional hazards regression as a pre-specified sensitivity analysis.

Continuous outcomes measured at baseline, 12 months, and end of study (LVEF, BNP, KCCQ) will be analyzed using ANCOVA, with the 12-month value as the dependent variable and adjustment for the baseline value, the randomization stratification variables (site and sex), and the pre-specified baseline covariates (age and baseline systolic blood pressure). The 12-month comparison is the primary timepoint for these secondary outcomes; the end-of-study comparison, which occurs at a participant-varying duration under the common close-out design, is analyzed analogously as a supportive analysis. Because LVEF, BNP, and KCCQ at 12 months are observed only in survivors, these analyses will be interpreted together with the mortality results, and sensitivity analyses (responder analyses that assign unfavorable values to participants who die, and multiple imputation under clinically plausible assumptions) will assess the influence of death-related and other informative missing data.

NYHA functional class, an ordinal outcome measured at baseline and 12 months and end of study, will be analyzed using ordinal logistic regression adjusted for baseline class, the randomization stratification variables (site and sex), and the pre-specified baseline covariates (age and baseline systolic blood pressure). Medication adherence outcomes (pill count and MARS-5), which are measured at baseline, 1, 6, and 12 months, and end of study, will be analyzed using linear mixed models with an unstructured covariance matrix to account for the repeated measures structure and within-subject correlation across timepoints. Persistence with assigned therapy will be analyzed using Kaplan-Meier methods and Cox regression for time to permanent discontinuation. Dose optimization, defined as the proportion achieving the target dose (Strength 3, or comparable individual GDMT doses in the comparator arm) at 6 months, 12 months, and end of study, will be analyzed using log-binomial or modified Poisson regression with robust variance. For the KCCQ, in addition to the ANCOVA of mean change, the proportion of participants achieving a clinically meaningful improvement (a ≥5-point increase) will be compared between arms using log-binomial or modified Poisson regression, with participants who die before the 12-month assessment classified as non-responders.

23. Missing Data

Missing data patterns will be examined by treatment group and time point. For time-to-event outcomes, the LWYY and Cox models account for censoring, and death is not treated as missing data. For continuous and ordinal outcomes (LVEF, BNP, KCCQ-23, NYHA class), values truncated by death are classified as undefined rather than unobserved. No imputation of post-death values will be performed. Robustness to genuinely unobserved missing data (i.e., missing among survivors) will be evaluated via multiple imputation by chained equations (MICE) for intermittently missing covariates and best-case/worst-case imputation scenarios for the primary composite.

24. Additional Analyses

The win ratio is a pre-specified secondary (sensitivity) analysis and is not the primary analysis. For each possible pair of participants (one from each treatment arm), compared over their shared follow-up time, outcomes are ranked in a fixed hierarchy: first cardiovascular death (the participant with the earlier death is the loss); then, for pairs not separated by mortality, the total number of heart failure hospitalizations (the participant with more hospitalizations is the loss). Pairs that cannot be separated at either level are counted as ties. The analysis will be stratified by the randomization strata (site and sex). The win ratio (wins in the HFrEF polypill arm divided by wins in the usual-care arm) will be reported with a 95% confidence interval and p-value, together with the win difference (net benefit) as a companion absolute measure.

As a separate exploratory analysis, an expanded win ratio will add the change in KCCQ-23 score as a third priority level below the clinical events, compared on the continuous difference. Subgroup analyses may examine treatment effects by sex, site, baseline NYHA class, and baseline LVEF, ischemic versus non-ischemic etiology, diabetes status, age, baseline eGFR, and background guideline-directed medical therapy at

enrollment.

Subgroup analysis results will be presented as forest plots with point estimates, 95% confidence intervals, and interaction p-values. No adjustment for multiplicity will be applied to subgroup analyses, and results will be interpreted as exploratory given both the inflated type I error rates for subgroup statistical tests and the limited power for interaction tests.

25. Harms

Safety outcomes will include serious adverse events according to Good Clinical Practice guidelines, adverse events of special interest, adverse events leading to drug discontinuation, and mean changes in serum potassium and creatinine. The proportion of participants with each adverse event of special interest, with any serious adverse event, and with an adverse event leading to discontinuation of heart failure medications will be summarized by arm with 95% confidence intervals and compared using risk ratios. Mean changes from baseline in serum potassium and creatinine at 12 months and end of study will be analyzed using ANCOVA adjusted for baseline values and the randomization stratification variables (site and sex), and the pre-specified baseline covariates (age and baseline systolic blood pressure).

26. Statistical Software References

Analyses will be conducted using R (version 4.0 or later) and SAS (version 9.4 or later).

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List of Abbreviations and Definition of Terms

AE: Adverse event
ANCOVA: Analysis of covariance
ARB: Angiotensin receptor blocker
BMI: Body mass index
BNP: B-type natriuretic peptide
DSMB: Data and safety monitoring board
DSMP: Data and safety monitoring plan
ECG: Electrocardiogram
eGFR: Estimated glomerular filtration rate
GCP: Good Clinical Practice
GDMT: Guideline-directed medical therapy
HF: Heart failure
HFrEF: Heart failure with reduced ejection fraction
ICH: International Council for Harmonization
ITT: Intention to treat
KCCQ-23: Kansas City Cardiomyopathy Questionnaire (23-item)
LVEF: Left ventricular ejection fraction
LWYY: Lin-Wei-Yang-Ying
MARS-5: Medication Adherence Report Scale-5
MRA: Mineralocorticoid receptor antagonist
NYHA: New York Heart Association
REDCap: Research Electronic Data Capture
SAE: Serious adverse event
SAP: Statistical Analysis Plan
SBP: Systolic blood pressure
SGLT2i: Sodium-glucose cotransporter 2 inhibitor