Statistical analysis plan for the DANHEART study
Date: 09JUN2026

Primary endpoint

The composite primary endpoint is defined as the time to the first occurrence of any of the following events:

H-HeFT: Death or hospitalization with worsening heart failure or an urgent visit resulting in intravenous therapy or metolazone therapy for heart failure or heart transplantation or implantation of a LVAD.

Met-HeFT: Death or hospitalization with worsening heart failure or an urgent visit resulting in intravenous therapy or metolazone therapy for heart failure or heart transplantation or implantation of a LVAD or acute myocardial infarction or stroke.

The unconditional power, based on the expected number of events, is presented in Table 1. The predicted study results for various observed hazard ratio, assuming proportional hazards, are presented in Table 2 in the Appendix.

Table 1: Sample size requirement. HR=hazard ratio assuming proportional hazards.

Study	Number of events	HR	Power
Met-HeFT	200	0.7	71%
Met-HeFT	200	0.67	81%
Met-HeFT	200	0.6	95%
H-HeFT	175	0.7	66%
H-HeFT	175	0.67	75%
H-HeFT	175	0.6	92%

Secondary endpoints

1. The total number events (first and recurrent) in the primary endpoint
2. Interaction analysis of the primary endpoint with the following subgroups: age (above/below median), sex, primary cause of heart failure (Ischemic heart disease vs. other) , previous hypertension, previous myocardial infarct, previous revascularization, NYHA class (three strata: I, II, III+IV), median LVEF, eGFR

(above/below median AND eGFR< 30, 30-60 and >60), NT-proBNP (above below median), blood pressure (mean, systolic, diastolic) (above/below median), heart rate (above/ below median), diabetes, HOMA insulin resistance index (above/below median AND tertiles: low/middle/high), body mass index (above/below median AND <30, 30-35, >35), HbA1c (above/below median AND <42, 42-47, ≥48), fasting p-glucose(above/below median AND <5.6, 5.6-6.9, ≥7.0), fasting p-insulin (above/blow median), triglyceride level (above/below median). Interaction analysis with the other treatment arm (Metformin or Hydralazine/ISDN)

3. Composite endpoint: The primary endpoint or coronary revascularization or non-coronary revascularization or limb amputation
4. Total death and death divided into following subcategories:
    - Progressive heart failure
    - Sudden cardiac death
    - Other CV death
    - Non-cardiovascular death
    - Cancer
    - Unknown
5. Hospitalization with worsening heart failure or an urgent visit resulting in intravenous therapy or metolazone therapy for heart failure, heart transplantation or LVAD implantation
6. Acute myocardial infarction
7. Stroke
8. Number of cardiovascular hospitalizations
9. Number of non-cardiovascular hospitalizations
10. Total number of hospitalizations
11. New onset diabetes
12. Lactic acidosis
13. Change in NT-proBNP from baseline to final follow-up
14. Change in HOMA-IR from baseline to final follow-up
15. Change in HbA1c from baseline to final follow-up
16. A per protocol (“as treated”) analysis of: a) the primary endpoint and b) the secondary endpoint “total number events (first and recurrent) in the primary endpoint” and c) other secondary events
17. Analyses of serial changes in HbA1c and blood pressure during the study period

Time to first occurrence of primary and secondary events will be compared between groups using Cox regression with treatment as the sole variable expressing the treatment effect using a hazard ratio. The proportional hazards assumption will be evaluated using log–log plots. The cumulative incidence function will be estimated using the Kaplan-Meier method for events including all course death and by the Aalen-Johansen method for events where death is a competing event. Recurrent primary events and hospitalizations will be compared between groups using the Ghosh-Lin model (Ghosh and Lin 2002) with treatment as the sole variable, expression the treatment effect using a mean ratio. The cumulative mean function will be estimated using the methods of Cook and Lawless (1997) and Ghosh and Lin (2000). Estimates with 95% confidence intervals will be presented and statistical tests comparing the treatment groups using the Wald method with significance level 5%.

Changes in biomarkers will be compared between groups using two-sample t-tests among patients with available data.

References

Cook, Richard J, and Jerald F Lawless. “Marginal Analysis of Recurrent Events and a Terminating Event.” *Statistics in Medicine* 1997;16 (8): 911–24.

Ghosh, Debashis, and Danyu Y Lin. “Marginal Regression Models for Recurrent and Terminal Events.” *Statistica Sinica*, 2002;663–88.

Ghosh, Debashis, and DY Lin. “Nonparametric Analysis of Recurrent Events and Death.” *Biometrics* 2000;56 (2): 554–62.

Appendix

Table 2: Predicted study results given observed hazard ratio (HR) and assuming proportional hazards.

Study	Number of events	HR	P-value
Met-HeFT	200	0.80	11.46%
Met-HeFT	200	0.75	4.19%
Met-HeFT	200	0.70	1.17%
Met-HeFT	200	0.67	0.46%
Met-HeFT	200	0.60	0.03%
H-HeFT	175	0.80	14.00%
H-HeFT	175	0.75	5.71%
H-HeFT	175	0.70	1.83%
H-HeFT	175	0.67	0.81%
H-HeFT	175	0.60	0.07%