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The DANish randomized, double-blind, placebo controlled trial in patients with chronic HEART failure (DANHEART): A 2 × 2 factorial trial of hydralazine-isosorbide dinitrate in patients with chronic heart failure (H-HeFT) and metformin in patients with chronic heart failure and diabetes or prediabetes (Met-HeFT)

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[1]General inquiries about this paper and the DANHEART study as well as specific questions about the Met-HeFT study to Henrik Wiggers.

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Declaration of interest:None relevant (investigator-initiated, non-commercial study)

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[2] Specific questions with respect to the H-HeFT study to Finn Gustafsson.

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Objectives The DANHEART trial is a multicenter, randomized (1:1), parallel-group, double-blind, placebo-controlled study in chronic heart failure patients with reduced ejection fraction (HFrEF). This investigator driven study will include 1500 HFrEF patients and test in a 2 × 2 factorial design: 1) if hydralazine-isosorbide dinitrate reduces the incidence of death and hospitalization with worsening heart failure vs. placebo (H-HeFT) and 2) if metformin reduces the incidence of death, worsening heart failure, acute myocardial infarction, and stroke vs. placebo in patients with diabetes or prediabetes (Met-HeFT).

Methods Symptomatic, optimally treated HFrEF patients with LVEF ≤40% are randomized to active vs. placebo treatment. Patients can be randomized in either both H-HeFT and Met-HeFT or to only one of these study arms. In this event-driven study, it is anticipated that 1300 patients should be included in H-HeFT and 1100 in Met-HeFT and followed for an average of 4 years.

Results As of May 2020, 296 patients have been randomized at 20 centers in Denmark.

Conclusion The H-HeFT and Met-HeFT studies will yield new knowledge about the potential benefit and safety of 2 commonly prescribed drugs with limited randomized data in patients with HFrEF. (Am Heart J 2021;231:137-46.)

Hydralazine – isosorbide dinitrate and contemporary heart failure treatment

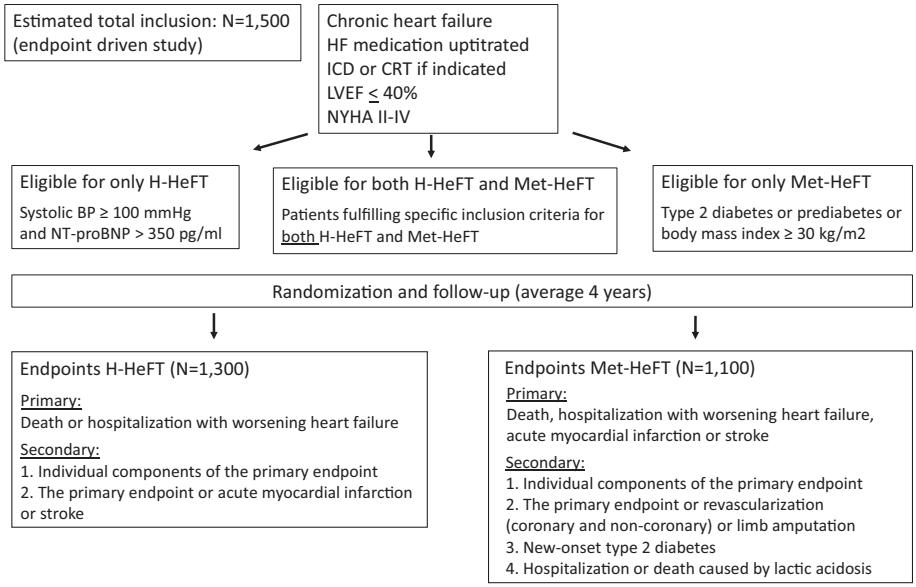
Heart failure is a common and deadly disease.[1,2] In patients with heart failure, hydralazine-isosorbide dinitrate (ISDN) effectively decreases filling pressures while increasing cardiac output[3] and was shown in early placebo controlled studies to reduce mortality in patients not treated with renin-angiotensin inhibitors.[4] In 2004, the A-HeFT study demonstrated a mortality reduction of 43% with the combination of hydralazine and ISDN given on top of established therapy.[5] The study population consisted of HFrEF patients of African descent and the therapy has never been tested in other populations on contemporary, optimal heart failure therapy. The main hypothesis of the hydralazine-isosorbide dinitrate in patients with chronic heart failure trial (H-HeFT) is thus to test if hydralazine in combination with ISDN can reduce mortality and hospitalization with worsening heart failure. Patients included in A-HeFT had relatively preserved systolic blood pressure of 126 mmHg despite uptitrated neurohormonal blockade. This is consistent with the fact that the response to ACE-inhibitors in African-American patients with heart failure and hypertension is less pronounced than in Caucasian patients.[6] The target dose of hydralazine-ISDN in the current study is similar to that used in A-HeFT, but it is conceivable that the dose achieved will be lower in this contemporary heart failure population receiving extensive vasodilator therapy.

Metformin treatment in patients with cardiovascular disease including heart failure

Metformin is a cornerstone in the glucose-lowering treatment in patients with type 2 diabetes (T2D) and today the drug is taken daily by millions of patients worldwide. In the UKPDS study of patients with T2D, metformin reduced diabetes-related death with 30%, acute myocardial infarction by 39%, coronary death by 50%, and stroke by 41% over a 10-year period in newly diagnosed overweight T2D patients without previous cardiovascular disease.[7] The drug has been first-line therapy in the treatment of T2D for decades, but recent guidelines[8] have downscaled the recommendation for metformin in T2D. This is partly because the metformin substudy of the UKPDS trial compared conventional therapy with metformin in 753 patients in a nested study design and that few patients were on randomized therapy after 5 years.[8,9] and there has been no randomized outcome trials to assess the effect of metformin on cardiovascular events. Furthermore, and most importantly, the recent large randomized clinical trials of sodium glucose co-transporter 2 (SGLT2)-inhibitors[10] and glucagon like peptide 1 (GLP1)-analogues[11] have provided strong evidence of a beneficial clinical effect of these newer drug classes. It must be kept in mind, though, that these new glucose-lowering drugs in most patients were tested on top of metformin.

Among HFrEF patients, 50% to 70% have either diabetes or prediabetes[12,13] and among HFrEF patients without overt diabetes, 3% to 10% develop new-onset diabetes yearly.[14,15] In heart failure patients, the presence of diabetes and insulin resistance is associated with reduced functional capacity[16] and a 50% increase in yearly mortality.[12,13,17,18] Registry studies show that metformin treatment is associated with improved prognosis in heart failure patients,[19-21] but obviously cannot correct for all confounders. Today, only 2 minor clinical randomized metformin studies have been conducted in HFrEF patients. In 58 insulin resistant HFrEF patients, treatment for 4 months of metformin-treatment did not improve exercise capacity or LVEF as compared with placebo.[22] In 36 prediabetic HFrEF patients, metformin treatment for 3 months reduced myocardial oxygen consumption by 17% as compared with placebo[23] suggesting a beneficial effect on the coupling between energy- and force-generation in the failing heart. The metformin in patients with chronic heart failure and

Figure 1



Overall study design and endpoints in the DANHEART study (including the 2 substudies H-HeFT and Met-HeFT).

diabetes or insulin resistance trial (Met-HeFT) will be the largest randomized study to date of the efficacy and safety of metformin in patients with prediabetes or diabetes and established heart disease. It will also be the first study in HFrEF patients powered to address the effect of metformin on clinical outcomes.

Study design

The DANHEART trial is an investigator-driven, multicenter, randomized (1:1), parallel group, double-blind, placebo controlled study in chronic heart failure patients. In the DANHEART trial, the 2 studies H-HeFT and Met-HeFT are combined in a 2 × 2 factorial design. The trial tests whether these treatments are superior to placebo. The existence of an effect modification in patients receiving both treatments (i.e. interaction) will be explored. In this event-driven study, it is estimated that 1300 patients and 1100 patients should be included in H-HeFT and Met-HeFT, respectively, and followed for an average of 4 years. Based on a pilot study in Danish heart failure clinics, it is expected that if 1500 patients are included in the DANHEART study 900 patients will be eligible for inclusion in both H-HeFT and Met-HeFT, 400 in H-Heft only, and 200 in Met-HeFT only. The overall study design is shown in Figure 1.

The study will be conducted according to the most recent approved study protocol, ICH-GCP guidelines and applicable regulatory requirements and legislation and it will be monitored by the GCP-units in Denmark.

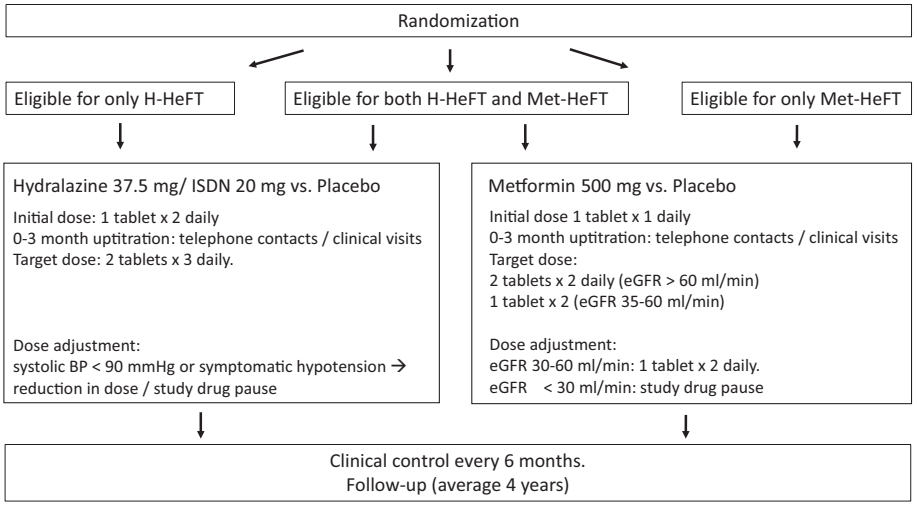
Patient population

Patients with symptomatic chronic heart failure are included and randomized at 20 public hospitals in this nationwide study in Denmark.

General inclusion criteria:

- Patients with chronic heart failure.
- NYHA-class II, III or IV.
- LVEF ≤40% within 12 months prior to screening (echocardiography should (i) be performed after uptitration in heart failure medication and (ii) LVEF from the most recently performed echocardiographic study should be used and (iii) LVEF must not be measured during rapid atrial fibrillation, i.e. heart rate >110/min), (iv) if treatment with ACE-inhibitor/ ARB is switched to treatment with Entresto, no new echocardiography is required (v) The echocardiography should be performed at least 3 months after CRT-implantation.
- Patients should be uptitrated to recommended or maximally tolerated dose of ACE-I/ARB/ARNI (unless contraindicated) and beta-blocker (unless contraindicated). If indicated, an aldosterone receptor antagonist should be given (unless contraindicated).
- A CRT device should be implanted, if indicated and accepted by the patient and patients with a CRT device should be treated for >3 months.
- Implantation of an ICD unit should be planned or already done, if indicated and accepted by the patient.

Figure 2



Study drug dosing, adjustment and control.

The patient can be included in the study before a planned ICD implantation has been performed.

- Informed consent.

Specific inclusion criteria for only H-HeFT and only Met-HeFT:

In the H-HeFT study, the main inclusion criteria are: systolic blood pressure ≥ 100 mmHg and NT-proBNP >350 pg/mL or BNP >80 pg/mL.

In the Met-HeFT study, patients must have a diagnosis of T2D, prediabetes or increased risk of developing T2D. This includes minimum one of the following: A previous diagnosis of T2D without metformin treatment within the last 3 months, HbA1c ≥5.5% (≥37 mmol/mol), fasting P-glucose ≥5.6 mmol/L, body mass index ≥30 kg/m^2 or an oral glucose tolerance test with a 2 hour P-glucose ≥7.8 mmol/L.

Detailed in- and exclusion criteria for both H-HeFT and Met-HeFT are shown in supplemental material (Table 1S).

Treatment and study schedule

Patients randomized in H-HeFT will receive either BiDil® (Hydralazine 37.5 mg/ ISDN 20 mg) or matching placebo. The initial dose is 1 tablet × 2 daily and target dose 2 tablets × 3 daily (Figure 2). Uptitration to 1 tablet × 3 daily is performed by a telephone contact. At a clinical visit, patients are uptitrated from 1 tablet × 3 daily to the target dose of 2 tablets × 3 daily, if tolerated. If systolic blood pressure is <100 mmHg, or patients report symptomatic hypotension, the dose is maintained on 1 tablet × 3 daily or reduced as judged by the investigator. During the trial, BiDil/placebo dose can be reduced due to hypotension, either systolic blood pressure <90 mmHg or symptomatic hypotension as judged by the investigator. BiDil and placebo tablets are delivered by Arbor Pharmaceuticals, LLC, Six Concourse Parkway, Suite 1800, Atlanta, GA 30328, USA. Packaging and labelling of study medication is done at the pharmacy at Aarhus University Hospital, Aarhus, Denmark.

Patients randomized in Met-HeFT will receive tablets containing either metformin hydrochloride 500 mg or matching placebo (Figure 2). In patients with eGFR >60 mL/min/1.73m^2 (MDRD formula), uptitration will gradually be done from a starting dose of 1 tablet × 1 daily to the target dose of 2 tablets × 2 daily. In patients with eGFR from 35 to 60 mL/min/1.73m^2 the metformin / placebo target dose is metformin 500 mg / placebo × 2 daily. Renal function is assessed at least every 6 months. If eGFR decreases to levels below 60 mL/min/1.73m^2 or 30 mL/min/1.73m^2, renal function (P-creatinine, P-urea, P-K^+, P-Na^+) is reassessed within 1 to 3 weeks. In case the repeated measurement confirms the decline in eGFR, the following changes are made: if eGFR is 30 to 60 mL/min, study drug is reduced to Metformin 500 mg/Placebo × 2 daily. If is eGFR<30 mL/min, study drug is paused and eGFR is rechecked at next visit. If the renal function has improved and is judged stable by the investigator, study drug can be reinstituted or dose increased. In case of severe acute illness, which involves very severe heart failure or severe worsening of renal function, study medication is paused and reinstituted again later if possible. When intravenous contrast agents are used, study medication is paused for 72 hours prior to and 48 hours after the use of contrast. Metformin and placebo tablets are delivered by Mawdsley Brooks and Co Ltd., Number Three, South Langworthy Road, PO Box 18,

Salford M50 2PW, England. Packaging and labelling of study medication is done at the pharmacy at Aarhus University Hospital, Aarhus, Denmark.

An overview of study drug uptitration, dose adjustment and follow-up is shown in Figure 2.

Endpoints

In H-HeFT, the primary endpoint is a combined endpoint of death or hospitalization with worsening heart failure compared to placebo. The secondary endpoints are: (i) individual components of the primary endpoint and (ii) a combined endpoint of death or cardiovascular hospitalizations (hospitalization with worsening heart failure, acute myocardial infarction, or stroke).

In Met-HeFT, the primary endpoint is a combined endpoint of death or cardiovascular hospitalizations (hospitalization with worsening heart failure, acute myocardial infarction, or stroke). The secondary endpoints are: (i) individual components of the primary endpoint, (ii) the primary endpoint or coronary revascularization or non-coronary revascularization or limb amputation, (iii) new-onset T2D and (iiii) hospitalization or death caused by lactic acidosis.

All reported endpoints from sites are adjudicated by an independent endpoint committee.

Study organization and study conduct

This study is an investigator-initiated trial with a steering committee responsible for the scientific content of the protocol and the conduct of the study and a Data Safety Monitoring Board will review the study (supplemental material, Appendix).

The trial is approved by the Danish National Ethical Committee and the Danish Data Protection Agency. The trial is registered at ClinicalTrials.gov Identifier NCT03514108, registration site Aarhus University Hospital, Denmark as well as in the EudraCT database number 2015-002150-12.

In March 2018, the first patient was enrolled. The inclusion period was initially planned to end in 2020, but due to problems with delivery of study medication all centers could not be initiated before autumn 2019. The drug delivery problem has now been solved and presently 20 sites are recruiting patients. During the most intense phase of the COVID-19 pandemic, the Danish Health authorities, the Danish Medicines Agency and the Danish GCP-units recommended a more lenient approach to study controls among patients included in randomized studies. We complied with this recommendation and converted clinical visits to telephone contacts if possible. Study medication was handed over to patients outside the hospital walls. Randomization of new patients was halted. The Danish authorities have now lifted these restrictions and presently the study is conducted without restraints.

Power calculation

We are planning a study with 1 control per experimental subject, an accrual interval of 2 to 4 years and additional follow-up of 3 years after the accrual of the last patient, i.e. an average follow-up period of 4 years. We expect a yearly withdrawal and drop-out rate of 4%.

H-HeFT

In a previous study, the median event time on the control treatment was 5 years, corresponding to a yearly event rate of 12%.[24] The true hazard ratio of control subjects relative to experimental subjects is assumed to be 1.33, corresponding to a treatment-associated 25% relative risk reduction. With a statistical power of 80% and 2-sided significance level of 5%, a sample size of 512 control and 512 experimental subjects are needed to reject the null hypothesis that the experimental and control survival curves are equal. Under these assumptions, we have estimated that 1300 patients in total will be sufficient to test the hypothesis. The study is event driven and the duration of follow-up period can be changed accordingly. Under the assumptions above, 391 events are needed to test the primary hypothesis.

Met-HeFT

The yearly hazard rate for the primary endpoint is expected to be 17%. This is based on recent observations in a Danish heart failure population.[25] The true hazard ratio of control subjects relative to experimental subjects is assumed to be 1.30, corresponding to 23% treatment-associated relative risk reduction. In previous registry studies, metformin treatment has been associated with reduction in death of 15% to 35%[19-21] and a reduction in hospitalizations around 20%.[20] With a statistical power of 80%, 2-sided alpha error 5%, a sample size of 456 subjects in each arm is needed. Under these assumptions, 1100 patients in total will be sufficient to test the hypothesis. The study is event driven and the duration of follow-up period can be changed accordingly. Under the assumptions above, 491 events are needed to test the primary hypothesis.

Based on previous data from heart failure clinics in Denmark,[12] it is anticipated that 15% of the patients in Met-HeFT will have T2D at the time of randomization and up to 10% will develop T2D yearly. Thus, the proportion of patients with a diagnose of T2D at final follow-up is expected to be between 27% and 55%.[14,15]

Statistical plan and data analysis

The primary endpoint will be analyzed using log rank statistics and presented as Kaplan-Meier plot. Analyses

Table I. Baseline characteristics of the first 296 patients included in the DANHEART study (H-HeFT and/or Met-HeFT).

	All patients	H-HeFT	Met-HeFT
N	296	177	247
General			
Women, n (%)	51 (17.2%)	36 (20.3%)	40 (16.2%)
Age (y)	67.9 (9.9)	70.2 (8.7)	67.8 (9.9)
BMI (kg/m^2)	29.6 (5.6)	29.2 (5.8)	29.6 (5.5)
NYHA functional class III or IV, n (%)	24 (8.1%)	17 (9.6%)	17 (6.9%)
LVEF (%)	31.4 (6.7)	31.1 (6.9)	32.1 (6.3)
Systolic blood pressure (mmHg)	120.3 (17.8)	125.3 (16.6)	119.4 (17.6)
Blood samples			
NT-proBNP (pg/mL)	691 [376-1595]	1015 [611-1900]	670 [296-1408]
- Sinus rhythm	589 [252-1038]	887 [596-1473]	521 [232-979]
- Atrial fibrillation	1228 [648-2391]	1271.0 [661-2461]	1140 [669-2235]
P-creatinine (µmol/L)	102.3 (31.5)	106.1 (35.2)	98.9 (24.6)
P-HbA1c (mmol/mol)	42 (8)	43 (10)	41 (6)
(%)	6.0 (1.1)	6.1 (1.4)	5.9 (0.9)
Fasting P-glucose (mmol/L)	6.1 [5.6-6.9]	6.2 [5.6-7.0]	6.1 [5.7-6.7]
Fasting P-insulin (pmol/L)	76 [51-122.4]	68 [45-107]	77 [52.8-121.7]
HOMA-IR index	2.9 [1.8-5.2]	2.6 [1.7-4.4]	3.0 [2.0-5.0]
Medical history			
Coronary artery disease, n (%)	163 (55.1%)	104 (58.8%)	133 (53.8%)
Atrial fibrillation, n (%)	103 (34.8%)	78 (44.1%)	79 (32.0%)
Known type 2 diabetes, n (%)	46 (15.5%)	40 (22.6%)	16 (6.5%)
Hypertension, n (%)	95 (32.1%)	76 (42.9%)	69 (27.9%)
Stroke, n (%)	25 (8.4%)	18 (10.2%)	21 (8.5%)
Heart failure treatment			
ACEI or ARB, n (%)	187 (63.2%)	99 (55.9%)	161 (65.2%)
ARNI, n (%)	103 (34.8%)	72 (40.7%)	82 (33.2%)
Beta-blocker, n (%)	286 (96.6%)	172 (97.2%)	240 (97.2%)
MRA, n (%)	215 (72.6%)	116 (65.5%)	188 (76.1%)
Diuretics, n (%)	199 (67.2%)	120 (67.8%)	163 (66.0%)
- Loop diuretics	192 (64.9%)	117 (66.1%)	157 (63.6%
- Thiazides	15 (5.1%)	8 (4.5%)	12 (4.9%)
Diuretic dose, furosemide equivalents (mg)	40 mg [40-80]	40 mg [40-80]	40 mg [40-80]
SGLT2-inhibitor, n (%)	12 (4.1%)	10 (5.6%)	4 (1.6%)
Lipid lowering drugs	215 (72.6%)	133 (75.1%)	175 (70.9%)
ICD, n (%)	111 (37.5%)	56 (31.6%)	94 (38.1%)
CRT-P, n (%)	12 (4.1%)	10 (5.6%)	9 (3.6%)
CRT-D, n (%)	46 (15.5%)	29 (16.4%)	36 (14.6%)

Data are presented as mean (± SD), median [IQR] or n (%).
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blockers; ARNI, angiotensin receptor neprilysin inhibitor; BMI, Body Mass Index; CRT, cardiac resynchronization therapy; HbA1c, Hemoglobin A1c; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro b-type natriuretic peptide; NYHA, New York Heart Association Classification; SGLT2, sodium glucose co-transporter 2.

are performed as time to first event. Analyses will be performed according to intention-to-treat. In addition, data will also be analyzed "as treated" population. Formal interim analyses are not planned. The existence of an effect modification in patients receiving both treatments will be explored by Cox proportional hazards model with terms for the interaction between Hydralazine and Metformin. If the term for interaction is non-significant, it will be removed from the model. Drop-outs and withdrawals from the study will be registered and these patients will be followed through the Danish Health Registries with respect to events. An additional per-protocol analysis will be performed. Post hoc subgroup analyses will be presented. These will be prespecified prior to trial termination. Already planned subgroup analyses (above vs. below median *or* between categories) include: age, sex, primary cause of heart failure (ischemic vs. non-ischemic), previous hypertension, previous myocardial infarct, previous revascularization, NYHA class, LVEF, eGFR, NT-proBNP, blood pressure (mean, systolic, diastolic), heart rate, diabetes, Homeostatic Model Assessment of Insulin Resistance

(HOMA-IR), body mass index, HbA1c, fasting p-glucose and triglyceride level.

Patient long-term outcome will be further investigated in a registry study after termination of the trial.

Results

As of May 2020, 296 patients have been randomized in the DANHEART study at 20 centers in Denmark. Baseline characteristics of these patients are shown in Table I. Characteristics of patients included in H-HeFT and Met-Heft, respectively, are also shown in Table I.

Discussion

The DANHEART study combines the H-HeFT and Met-HeFT in a cost-effective, factorial design. This design makes it possible to investigate 2 different treatments that have independent effects. Thus, it is not expected that there will be an interaction between the 2 treatments. The design makes it possible to test for interactions, but will most likely be underpowered to give definite answers concerning this. The benefit of the design is the test of 2 relevant research questions that will most likely never be investigated otherwise because there is only limited commercial interest in the study drugs. Thus, our study aims to yield new knowledge about the potential benefit and safety of 2 commonly prescribed drugs with limited randomized data in HFrEF patients on optimal, contemporary medication.

Unexpectedly, more patients are currently enrolled in Met-HeFT than H-HeFT. The estimated distribution of patients in the 2 substudies was initially derived from a pilot study. A possible explanation of this deviation could be the implementation of treatment with sacubitril/valsartan and SGLT2-inhibitors during the last years. These drug classes are prescribed to approximately 40% of the patients included in this trial. They reduce blood pressure and NT-proBNP and limit inclusion in the H-HeFT study arm.

We chose include patients irrespective of the occurrence of atrial fibrillation, although this arrhythmia is associated with higher levels of NT-proBNP. A similar approach has been used in the PARADIGM-HF and DAPA-HF trials, although in the latter trial higher levels of NT-proBNP was requested in patients with atrial fibrillation. In those 2 studies the proportion of patients with atrial fibrillation was 37% and 38%, respectively. In DANHEART this proportion is 35% and thus, similar to recent heart failure trials and to what has been observed in cross-sectional studies in heart failure patients.[26]

The hydralazine-isosorbide dinitrate hypothesis (H-HeFT)

Patients included in the A-HeFT study[5] had relatively preserved blood pressure despite uptitrated neurohormonal blockade. This is consistent with the fact that the response to ACE-inhibitors in African-American patients with heart failure and hypertension is less pronounced than in Caucasian patients.[6] The most recent European guidelines mandate that hydralazine-ISDN should be considered in HFrEF patients in self-identified black patients with HFrEF and NYHA class III-IV despite optimal medical therapy.[27] In addition, this may be considered in HFrEF patients not able to tolerate renin-angiotensin-aldosterone system (RAAS) inhibitors.[27] The H-HeFT study should be able to qualify these guidelines for non-black patients and to test the effect in a study population on contemporary medication with less severe heart failure. Specifically, among the included patients in H-HeFT to date, 90% are in NYHA class II, 40% are treated with angiotensin receptor neprilysin inhibitors (ARNI) and 54% have received an implantable cardiac device. Finally, H-HeFT will provide contemporary data for the use in the subgroup patients not tolerating RAAS inhibitors as they are not excluded from the trial, even if they are expected to constitute a small proportion of patients (Table I).

The metformin hypothesis (Met-HeFT)

The beneficial effects of metformin in the UKPDS study[7] occurred in spite of similar blood glucose levels suggesting that metformin has pleiotropic effects beyond blood glucose control. This could be mediated through increased insulin sensitivity, reduced insulin levels, reduced hypercoagulability, improvement of the lipid profile, vasodilatation, weight loss, activation of intracellular cell survival pathways[28] and direct mitochondrial effects.[29] This hypothesis was corroborated by the ORIGIN study which showed that reduction in blood glucose levels per se did not reduce cardiovascular events in the studied population.[30] However, as mentioned previously, the randomized data on metformin treatment in patients with documented cardiovascular disease are scarce and there is a definite need for more randomized data.[9]

Heart failure patients treated with metformin can develop lactic acidosis and the drug was previously not recommended in these patients. However, registry studies report that the risk of lactic acidosis is similar in patients treated with and without metformin.[31] A large meta-analysis of metformin in prospective comparative trials and observational cohort studies conclude that metformin is not associated with an increased risk of lactic acidosis and that lactate levels are unaffected by treatment.[32] For that reason, the ESC, EASD and FDA now approve the use of metformin in heart failure patients. The safety data on metformin in heart failure patients are solely derived from registry data with an inherent risk of confounding. In the Met-HeFT trial, safety issues including the risk of lactic acidosis will be addressed for the first

time in a large clinical, randomized trial with adjudicated events.

In patients with insulin resistance, metformin reduces the occurrence of new-onset diabetes with 31%.[33] Insulin resistance and deranged glucose-, lipid- and protein-metabolism can promote progression of heart failure and loss of lean body mass. Therefore, metformin treatment that counteracts these metabolic abnormalities can have beneficial effects.[16,18] As compared with the DAPA-HF trial,[10] the proportion of Met-HeFT patients at randomization with T2D is presently low (41% vs. 7%). However, the Met-HeFT study population has a median HOMA-IR index of 3.0 signifying a high degree of insulin resistance.[34] It is therefore expected that the proportion of patients with T2D will increase throughout the study period due to development of de-novo diabetes.[14,15] In addition, the proportion of metformin-naïve T2D patients eligible for randomization is likely to increase after publication of the new guidelines on glucose-lowering therapy in T2D. They recommend that metformin is no longer first choice treatment in T2D patients with cardiovascular disease.[8]

We included patients with HbA1c ≥5.5% (37 mmol/mol) which is below the definition of prediabetes by the American Diabetes Association (5.7%, 39 mmol/mol). We chose this cutoff because the risk of death in heart failure patients increases before the development of overt diabetes.[13] In patients who have developed diabetes, glucose lowering therapy has been disappointing with respect to changing the prognosis.[35] One of the ideas behind the design of Met-HeFT is therefore that early intervention to prevent or postpone the development diabetes can improve outcome. A similar threshold of HbA1c ≥5.5% has been used in the Glucose Lowering In Non-diabetic hyperglycaemia Trial (GLINT) – Glucose lowering in those at risk of diabetes (GLINT) trial.[36] The patients included in MetHeFT have an average HbA1c of 43 mmol/mol (6.1%), i.e. the majority of patients fulfill the ADA criteria for prediabetes.

The use of implantable devices in 57% of patients is higher than in most previous trials, e.g. 21% in PARADIGM-HF and 34% in DAPA-HF.[37,38] In addition, the use of diuretics in only 67% of the patients is lower than in the PARADIGM-HF (80%) and DAPA-HF trials (93%). This is conceivably due to a combination of more use of CRT-devices (20%), ARNI (35%) and to lower NT-proBNP at inclusion in the DANHEART population.

Estimated event rate and power as compared with other contemporary heart failure trials

In contemporary randomized heart failure studies, the event rate of a composite endpoint of death and cardiovascular death in the placebo groups has ranged between 11.6 and 12.1 percent per year in DAPA-HF and PARADIGM-HF.[37,38] The inclusion criteria in these studies have requested higher NT-proBNP and lower LVEF than the present H-HeFT study. Compared with the PARADIGM-HF and DAPA-HF studies, the patients presently included in H-HeFT have similar LVEF (31% vs. 30%-31%) but lower NT-proBNP (1000 ng/L vs 1400-1600 ng/mL). However, we have included patients of older age (70 years vs 64-66 years) and therefore believe that an event rate of 12% in our composite endpoint of total death and worsening with heart failure is realistic. The study is event driven and the duration of follow-up period can be changed accordingly.

In the Met-HeFT study the yearly hazard rate for the primary endpoint is expected to be 17%. This is based on data in a Danish heart failure population.[25] In that study a composite endpoint of death and hospitalization because of worsening of heart failure, myocardial infarction, stroke, unstable angina, cardiac syncope, hypertension and arrhythmia was 17%/year. In the present study, admission due to cardiac syncope, hypertension and arrhythmia are not included in the primary endpoint. However, the event rate in the Met-HeFT population is assumed to be 17%/year due to inclusion of patients with diabetes and insulin-resistance (who are known to have an increased event rate) and exclusion of NYHA class I patients who constituted 20% of the study population in the paper by Schou et al..[25] The study is event driven and the duration of follow-up period can be changed accordingly.

We estimate that 4% of patients become off study drug per year. In the DAPA-HF trial,[38] 11% of study subjects were off study drug after an average 18 month follow-up, corresponding to 7% of patients off study drug per year. In the PARADIGM-HF trial,[37] after 27 month average follow-up, 19% of patients were off study drug, i.e. 8% off study drug per year. It is possible that our estimate is too low. However, the average follow-up in our study is at least 4 years. The proportion of patients becoming off study drug is expected to decline during the study period. In comparison, the SEAS study[39] with an average follow-up period of 4.3 years had a 19% of patients off study drug, corresponding to 4% of patients off study drug per year.

In this investigator driven study without commercial interest from medical companies, we have achieved funding to detect what we believe are clinically meaningful treatment effects. We have stipulated a detection of a risk reduction of 25% in H-HeFT and 23% in Met-HeFT (please refer to Power calculation). In addition, the trial with yield knowledge about safety and tolerability of the study drugs in a contemporary heart failure population. There are risks in long-term trials in terms of more drop-outs and more competing events. Although all-cause mortality is a key component of the primary endpoint, this may become driven by cancer and

other causes of death. However, we aim to perform a trial with a high external validity that can be extrapolated to everyday clinical practice.

Conclusion/summary

There are limited randomized data on the effects of hydralazine-ISDN and metformin in HFrEF patients receiving contemporary heart failure treatment. Thus, the H-HeFT and Met-HeFT studies aim to yield knowledge about the potential benefit and safety of these 2 commonly prescribed drugs in HFrEF patients. Specifically, H-HeFT will be the first large scale, randomized study of hydralazine-ISDN since the A-HeFT trial and it will test this treatment in a broader population of HFrEF patients. Furthermore, the Met-HeFT study will be the largest randomized study to date of metformin in patients with established heart disease and the first study in HFrEF patients powered to address clinical outcomes.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2020.09.020.

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