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ARTICLE

Effect of metformin and empagliflozin on myocardial function in insulin-resistant patients with heart failure: rationale and design of the METRIS-HF-DZHK18 trial

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Abstract

Impaired energy metabolism contributes to clinical severity, disease progression and to outcome in heart failure (HF). Insulin sensitivity (IS) is a key factor in the control of energy substrate utilisation and energy efficiency in cardiac and skeletal muscle. Impaired IS, or insulin resistance, is a common finding in HF and has been shown to predict morbidity and mortality in patients with heart failure with reduced and mildly reduced ejection fraction (HFrEF, HFmrEF). Despite its pathophysiologic relevance, IS has not been explored as a therapeutic target in HF. The objective of the METRIS-HF trial is to evaluate the effect of the insulin sensitizer metformin on top of standard care on myocardial contractility and functional capacity in insulin-resistant patients with HFrEF and HFmrEF in comparison to empagliflozin and placebo. METRIS-HF is an investigator-initiated, multicentre, randomized, double-blind, placebo-controlled, double-dummy trial to enrol HF patients with reduced ejection fraction and insulin resistance into three parallel treatment arms in a 1:1:1 ratio to receive metformin (1000 mg bd), empagliflozin (10 mg od), or double placebo, on top of standard heart failure therapy. The intervention lasts 24 weeks, followed by a 28-week follow-up period. The primary endpoint is the change in left ventricular global longitudinal strain (GLS) at 24 weeks. Key secondary endpoints include measurements of functional and symptomatic status such as 6-minute walking distance, NYHA functional class, patient global assessment (PGA), and health-related quality of life (EQ-5D, KCCQ). Exploratory endpoints include metabolic, inflammatory, functional, and imaging-based biomarkers. Safety is assessed by adverse and serious adverse events throughout the trial. The METRIS-HF-DZHK18 trial will investigate the effect of metabolic treatments to improve insulin sensitivity in patients with HFrEF and HFmrEF to provide mechanistic insights into efficacy of metabolic interventions in heart failure.

Key words: heart failure; insulin resistance; metformin; empagliflozin; global longitudinal strain; randomized clinical trial.

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Introduction

Heart failure (HF) remains a leading cause of morbidity, hospitalisation and premature mortality worldwide. Despite substantial therapeutic advances, many patients continue to experience reduced functional capacity and poor prognosis. Metabolic impairment and particularly impaired energy metabolism of both, the myocardium and skeletal muscle is a main pathophysiologic principle that contributes to impaired functional capacity, symptomatic status, disease progression and to poor prognosis.[1,2]

Insulin resistance is a common finding in HF and a key upstream driver of impaired energy metabolism in HF and is associated with diverted substrate utilisation, increased ROS accumulation, endothelial dysfunction and reduced efficacy of both cardiac and skeletal muscle function.

Insulin resistance affects an estimated 43-61% of patients with HF, both with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF).[3,4] Notably, insulin resistance occurs in HF as a distinct metabolic feature within HF pathophysiology and independent of type 2 diabetes mellitus (DM).[2] In turn, DM is a common comorbidity of HF and insulin resistance as the underlying metabolic disturbance of type 2 DM may represent a pre-diabetic state.[5] Insulin resistance in patients with HF is associated with worse exercise capacity, higher natriuretic peptide levels, and increased mortality.[6] Improving metabolic efficacy by targeting insulin resistance seems a promising therapeutic target in patients with HF.[7] For decades, guideline-recommended HF therapies with prognostic benefit targeted exclusively haemodynamic and neurohormonal pathophysiological pathways. Only recently, sodium-glucose cotransporter 2 (SGLT2) inhibitors emerged as a novel treatment option targeting downstream glucose metabolic balance. No treatment option has been established that directly targets impaired insulin sensitivity as the upstream signalling mechanism of impaired energy metabolism in HF independently of DM.

Metformin, a well-known insulin sensitizer, has demonstrated favourable effects on cardiovascular outcomes and myocardial energetics in observational studies. Metformin modulates several metabolic pathways: activation of AMPK, inhibition of hepatic gluconeogenesis, increased peripheral glucose uptake, reduced lipid accumulation, and improved mitochondrial function and substrate utilization.[8] Observational studies report a prognostic benefit of metformin in HF with DM.[9] The potential effect of metformin to improve insulin sensitivity in patients with HF independent of DM has been investigated in few small or pilot studies with inconclusive results.[10-12] Controlled trials are needed to investigate potential beneficial effects of metformin in HF patients with insulin resistance.[13]

SGLT2 inhibitors have emerged as effective treatment in HF, irrespective of diabetic status.[14] The main mechanism is the increase in renal glucose excretion by inhibition of the renal sodium and glucose reabsorption. This downstream effect to reduce the glucose load may account for further interactions of metabolic pathways including substrate shift and rebalanced energy metabolism which may contribute to the clinical benefit in patients with HF.[15] Moderate beneficial effects of SGLT2 inhibitors on insulin sensitivity have been described in diabetic[16] and HF[17,18] models. However, the potential effect of SGLT2 inhibitors on insulin resistance and improved energy utilisation, potentially resulting in improved contractile efficacy in clinical HF has not been investigated. A direct comparison of metformin and SGLT2 inhibitors, particularly in non-diabetic HFrEF patients with insulin resistance, is lacking. The METRIS-HF-DZHK18 trial investigates the hypothesis that improved insulin sensitivity in the heart translates into improved energetic efficiency and functional capacity. Specifically, the study aims to investigate if treatment with the insulin sensitizer metformin on top of standard treatment for HF can improve myocardial contractility, functional status, and metabolic parameters in insulin-resistant patients with HFrEF or HFmrEF in comparison to empagliflozin or placebo. This protocol article outlines the study rationale, design, endpoints, and planned analyses.

Study design and methods

The METRIS-HF-DZHK18 trial (Metformin and Empagliflozin for Targeting Insulin Resistance in Heart Failure) is an investigator-initiated, multicentre, randomized, double-blinded, placebo-controlled, double-dummy clinical trial. The study aim is to evaluate the efficacy of metformin compared with empagliflozin and with placebo, to improve myocardial contractile function in patients with chronic heart failure with reduced or mildly reduced ejection fraction (HFrEF or HFmrEF) and with documented insulin resistance. METRIS-HF is funded by the German Centre for Cardiovascular Research (DZHK) with further financial support from Boehringer Ingelheim, and conducted under the Declaration of Helsinki, Good Clinical Practice (ICH-GCP), and the appropriate local legislation(s). The legal sponsor is Charité Universitätsmedizin Berlin. The trial is approved by the Ethics Committees of all participating sites. The trial is registered in the EU Clinical Trials Register (EudraCT 2017-004149-26).

Patient population

METRIS-HF recruited patients with stable symptomatic HFrEF or HFmrEF (LVEF <50%) in NYHA class II or III on guidelines-recommended HF therapies and with insulin resistance. Insulin resistance was assessed by HOMA-IR index using fasting blood sampling for measurement of glucose and insulin. Inclusion criteria and exclusion criteria are summarized in Table 1.

Study design and procedures

The trial consists of an intervention period of 24 weeks in a double-blinded, double- dummy design, followed by a 28-week follow-up phase. Eligible patients undergo a screening visit 2 weeks prior to randomization. Patients are randomly assigned to receive either metformin or empagliflozin or placebo

Table 1. Inclusion and exclusion criteria.

Inclusion criteria
• Symptomatic heart failure (NYHA II-III) in stable ambulatory condition
• Patients with the diagnosis of HF for >6 months
• Left ventricular ejection fraction (LVEF) <50%
• 6-minute walking distance of <450 m
• Elevated natriuretic peptides (BNP >100 pg/mL or N-terminal-proBNP >300 pg/mL)
• Medical treatment for HF according to current standards in individually optimized doses
• Evidence of insulin resistance (assessed by HOMA-IR ≥2.0)
• Signed written informed consent
• Age ≥18 years
Exclusion criteria
• Acute decompensated HF requiring acute intravenous therapy
• Current treatment with metformin or empagliflozin
• Known hypersensitivity or contraindication for metformin, empagliflozin
• Type 1 diabetes or uncontrolled type 2 diabetes (HbA1c ≥7.0%)
• Diagnosed DM or existing medical treatment for DM
• Impaired kidney function >CKD stage III (GFR <30 mL/min/1.73m^2)
• Acute systemic illness, malignancy, inflammatory disease, requiring antibiotic therapy, immune-suppressive - or steroid therapy
• Participation in another interventional clinical trial during this study or within 30 days before entry into this trial.
• Subjects who are legally detained in an official institution
• Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation
• For female patients of reproductive potential: Unwilling to agree to use a highly effective method of contraception (Pearl index <1) throughout the study period
• Any clinical condition that limits the life expectancy <1y

BNP, B-type natriuretic peptide; DM, diabetes mellitus; CKD, chronic kidney disease; GFR, glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction; HOMA-IR, homeostasis model assessment of insulin resistance, LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

on top of standard medical care. Metformin is administered with a starting dose of 500 mg bd and up-titrated after 2 weeks to 1000 mg bd if well tolerated. The study was initially designed as a two arm interventional study comparing metformin and placebo. Shortly after trial initiation, SGLT-2 inhibitors were approved in Germany for first line treatment in patients with HF regardless of DM. At the same time, the COVID-19 pandemic caused a massive strain on healthcare services and, due to quarantine measures, a forced interruption of many clinical trials - including those conducted at the study sites participating in the METRIS-HF trial. It was therefore decided by the steering committee to account for the emerging novel treatment option with SGLT2-inhibitors and to extend the study for an additional study arm for direct comparison of metformin with an SGLT2-inhibitor and with placebo. The enforced interruption of enrolment for the study was therefore used to amend the protocol and expand the study treatment regimen and logistics to a three-arm interventional trial. Empagliflozin was administered at a dose of 10 mg od throughout the study treatment period. Patients in one treatment arm received a placebo matching the concomitant study medication, patients in the placebo arm received placebo matching both study medications (double-dummy). All patients continue standard HF medication as per ESC guidelines. The flow chart of the study is shown in Figure 1. The visit schedule is shown in Table 2.

All cardiac magnetic resonance imaging (CMR) was performed at a 1.5 Tesla MRI (Philips Ambition, Philips Healthcare, Best, The Netherlands). Cine images were acquired in cardiac short-axis, two-, three- and four chamber view orientations using a retrospectively gated cine-CMR using a steady-state free precession (SSFP) sequence. All acquired images were analyzed offline by experienced CMR investigators blinded to the treatment of the participants in accordance with current SCMR consensus recommendations for the standardized image interpretation and post-processing in CMR using dedicated software (Medis Suite RE 4.0, Medis Medical Imaging Systems B.V., Leiden, The Netherlands). Left ventricular function and volumes were quantified as per the recommendation of the SCMR in a whole short axis (SAX) cine stack.[19] Endo- and epicardial borders were contoured in the end-diastolic and end-systolic phase with papillary muscles included in the left ventricular volumes.

Echocardiography studies were performed by specifically trained personnel. For quality assurance, data integrity and robustness, imaging followed a predefined standard protocol and local investigators had to be approved based on sample recordings submitted to the core echo lab and approved by an expert echocardiographer. All echo images are obtained on either GE Vivid E95 (Horten, Norway) or Philips EpiQ7 machines and analyses of echocardiography imaging are made by a single experienced echocardiographer in bulk assessment of the accumulated records at the end of the trial (TomTec Arena; TomTec Imaging Systems GmbH, Unterschleissheim, Germany). The assessing echo-reader is blinded to the study treatment assignments.

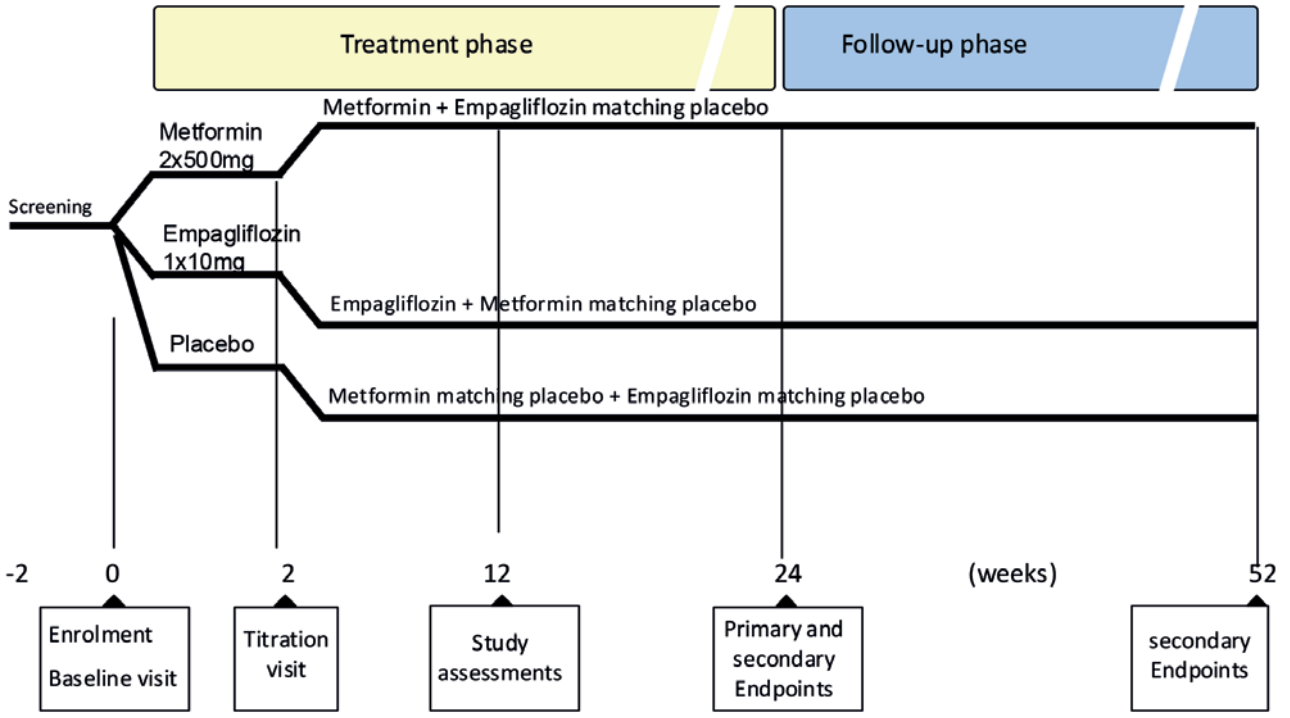

Figure 1. METRIS-HF study flowchart. Schematic overview of patient enrolment, randomization, treatment arms, and visit schedule including assessment time points.

Table 2. Visit schedule and study procedures.

Visit type	Screening	Enrolment	Baseline	Titration	Study assessments	End of treatment	Follow-up
Time frame (weeks, and visit window)	-2	0	0	2±2 d	12±2 w	24±2 w	52±2 w
Inclusion/exclusion criteria	x	x					
Signed informed consent		x					
Randomisation		x					
Current medication			x				
Medical history			x				
Physical examination			x		x	x	x
ECG			x			x	x
Echocardiography			x			x	
6-minute walking test			x		x	x	x
Fasting blood sample (lab* and biobank)			x		x	x	x
Insulin resistance	x		x		x	x	x
Quality of life assessment			x		x	x	x
Cardiac magnetic resonance imaging			x			x	
Start study medication			x				
Up-titration#				x			
Dispense study medication			x		x		
Primary endpoint						x	
Secondary end exploratory endpoints						x	
Safety blood test			x		x	x	
Adverse event recording			x	x	x	x	x
Electrophysiology recording						x	x

*Laboratory assessments: eGFR, insuline, glucose, NT-pro BNP, small blood count, HbA1c, sodium, potassium, ferritin, transferrin, transferrin saturation, AST/GOT, ALT/GPT, alkaline phosphatase, creatinine, creatinine-clearance, triglyceride, LDL-cholesterol, HDL-cholesterol, total-cholesterol, uric acid, bilirubin, hs-CRP (for baseline the laboratory results may be dated 1 month before); #titration step performed in patients with a GFR >44 mL/min/1.73 m^2 only.

Symptom-targeted physical examination and NYHA class status are assessed at each study visit and functional capacity will be assessed be 6-minute walking test (6MWT). Throughout the follow-up period, patients continue to receive their standard therapy for HF, and medical emergencies are treated according to local protocols, at the discretion of the treating physician. The patient's well-being in addition to the occurrence of adverse events and/or hospitalizations is evaluated, and the EuroQol-5D (EQ-5D) and Patient Global Assessment questionnaires are completed.

Study endpoints

The principal objective of this trial is to determine if treatment with the insulin sensitizer metformin or with the SGLT2-inhibitor empagliflozin may exert a beneficial effect on the myocardial contractile function of the left ventricle as compared to placebo in patients with HF with reduced LVEF. The primary endpoint is change in left ventricular global longitudinal strain (GLS) from baseline to week 24, assessed by speckle-tracking echocardiography.

Main secondary endpoints include measurements of functional capacity (change in 6MWT and NYHA functional class) as well as patient well-being and health-related quality of life (QoL) assessments (change in EQ-5D and KCCQ scores) and assessments of biomarkers of HF severity and insulin sensitivity (NT-proBNP levels, HOMA-IR index). Explorative endpoints relate to imaging based measures of myocardial functional capacity (early and late diastolic transmitral flow velocity, early diastolic mitral annular velocity, left atrial volume index, systolic ejection time, and strain analysis for global longitudinal strain). Safety endpoints address adverse and serious adverse events as well as lab measurements of deterioration of renal function, lactate levels and other safety markers. All endpoints are listed in Table 3. All laboratory assessments are performed at certified labs. Study data are collected using electronic case report forms (eCRFs).

Sample size rationale and statistical analyses

Randomisation for study arms is performed centrally using a computerised system initially in a 1:1 proportion, after extension in a 1:1.5:1 proportion. Patient randomisation will be performed as block randomisation stratified by study centre.

A sample size of 51 patients per group has been calculated to yield a power of 80% at a one-sided significance level of 2.5% given a treatment difference of 11% of the primary endpoint which is considered a clinically and prognostically meaningful effect. Previous reports on treatment effects on GLS ranged from 11%-37% improvement.[20,21]

The primary endpoint LV global longitudinal strain (GLS) will be analysed by means of Gaussian linear model for repeated measures (so-called MMRM) with treatment group (metformin, empagliflozin, placebo), time (week 12, week 24), treatment-by-time interaction, study centre and presence of DM as factors and baseline GLS as covariate. The primary comparison is metformin vs. placebo. A key secondary comparison is metformin vs. empagliflozin. The error terms are assumed to follow a multivariate normal distribution with unstructured covariance. Least squares mean changes from baseline will be reported for all groups with 95% confidence interval (CI) as well as the difference between the least squares treatment group means with 95% CI and p-value testing the null hypothesis of no treatment effect. The primary endpoint will be assessed by echocardiography for all patients. A one-sided p-value smaller than 2.5% will be considered statistically significant. Although the model described above is robust to a certain extend to missing data, sensitivity analyses will be performed as supporting analyses including multiple imputation to investigate the sensitivity of the results to missing data assumptions. In the primary analysis, all data from both design stages, namely first with randomisation to two groups and then to three groups, will be pooled. In supporting analyses, potential differences in the patient populations between the

Table 3. Primary and secondary outcomes.

Primary efficacy endpoints
• Change in global longitudinal strain (GLS) of the left ventricle (LV) after 24-week therapy.
Secondary endpoints
• Change in 6min-walking distance from baseline to 24 weeks
• Patient global assessment (PGA) from baseline to 24 weeks
• Change in 6 min walking distance from baseline to 52 weeks
• Patient global assessment (PGA) from baseline to 52 weeks
• Change in NYHA functional class from baseline to 24 weeks
• Change in QoL assessed by EQ-5D and Kansas City Cardiomyopathy Questionnaire (KCCQ) from baseline to 24 weeks
• Change in plasma levels of brain-type natriuretic peptides (BNP) from baseline to 24 weeks
Other exploratory endpoints (at 24 weeks and at 52 weeks)
• Change in echocardiographic measures of LV function and morphology
• Change in insulin sensitivity (HOMA-IR index)
• Change in MR measures of LV function and structure
• Changes in plasma levels of kidney function, liver function and inflammation
• Decrease of lymphocytic pro-inflammatory mediators

HOMA-IR, homeostasis model assessment of insulin sensitivity.

design stages will be explored to exclude a relevant patient selection bias. All subjects will be analysed as randomized, regardless of the actual treatment received following the intention-to-treat principle.

Continuous secondary endpoints will be analysed as the primary analysis described above and ordered categorical secondary outcomes will be analysed using rank-based methods for longitudinal data. In supporting analyses additional important baseline variables, including NYHA class and LVEF will be considered for inclusion in the regression models, in particular if baseline imbalances are apparent between the treatment groups. For recurrent events and to account for variable follow-up times event rates will be reported with rate ratios comparing verum with placebo control and 95% confidence intervals. We will use Poisson regression models with adjustment for overdispersion (or negative binomial regression models) with offset for follow-up time and possibly a mixture component to account for zero-inflation. For events of particular interest Kaplan-Meier curves stratified by treatment group will be computed and compared by log-rank tests. The analyses of the secondary and safety endpoints have an exploratory character and will therefore not be adjusted for multiple testing. The primary analysis population is the intention-to-treat population. The analysis population, subgroup analyses as well as all other details will be defined in the Statistical Analysis Plan which will be finalized prior to unblinding. All statistical analyses will be carried out using SAS software (SAS Institute Inc., Cary, NC, USA) or the R package.

Study committees and quality assurance

A structured trial governance has been implemented to ensure scientific and procedural integrity. The Steering Committee is responsible for overseeing scientific strategy, clinical relevance, and study coordination. A Data Safety Monitoring Committee (DSMC) will be established as an independent board responsible for periodic safety review. The DSMC follows a predefined charter and may recommend trial continuation, modification, or termination. Quality control is ensured by central trial monitoring according to a dedicated monitoring plan. This includes: on-site and remote monitoring, source data verification (SDV), data queries and validation *via* eCRF, and central oversight by the sponsor institution (Charité). Central core imaging laboratories perform the analysis of imaging assessments.

Discussion

Heart failure with reduced ejection fraction remains a major contributor to morbidity and mortality worldwide. Despite therapeutic advances, including the implementation of angiotensin receptor-neprilysin inhibitors, beta-blockers, mineralocorticoid receptor antagonists, and recently SGLT2 inhibitors, many patients continue to experience significant functional limitations and progressive disease. This phase IV study aims to provide novel pathophysiologic insight in the recently emerging novel treatment principle in patients, that targets the impaired metabolic capacity of the myocardium in order to improve metabolic efficacy and subsequently functional capacity.[22] The concept of metabolic failure as an underlying principle of the failing heart has long been established[1]. However, until recently no treatment options were available that specifically target the impaired metabolic capacity. In fact, for decades medical treatments with a proven prognostic impact targeted exclusively the overactivated neuroendocrine system, including increased sympathetic and renin-angiotensin-aldosterone axes, that is a major upstream pathophysiologic principle in heart failure. This includes ß-blockers, ACE inhibitors, angiotensin receptor blockers, aldosterone antagonists and neprilysin inhibitors.

Impaired insulin sensitivity has been recognised as a metabolic characteristic of HF that develops independently of the comorbidity of DM and represents an intrinsic feature of HF pathophysiology and potentially modifiable pathophysiological target in patients with HF.[2]

Insulin resistance is prevalent in a substantial proportion of patients with HFrEF, with reported rates ranging from 40% to over 60%, even in the absence of overt diabetes mellitus. It has been independently associated with reduced exercise tolerance,[23,24] impaired myocardial efficiency,[25] elevated natriuretic peptide levels,[26] and increased mortality.[6] However, insulin resistance is not currently targeted independent of DM by any approved heart failure therapies, and robust evidence on whether metabolic intervention can improve myocardial function and clinical status is lacking.

The METRIS-HF trial aims to addresses this unmet need by investigating two agents with distinct insulin-sensitizing properties: metformin, a biguanide commonly used in type 2 diabetes, and empagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor with proven benefits in heart failure populations.[14,27] Both agents are mechanistically attractive in the context of heart failure but differ in their metabolic profiles and clinical evidence base.

Metformin improves insulin sensitivity primarily by suppressing hepatic gluconeogenesis and enhancing peripheral glucose uptake. In preclinical studies and small clinical trials, metformin has been shown to improve myocardial energy efficiency, reduce myocardial fibrosis, and attenuate oxidative stress.[12,28,29] Observational data suggest improved outcomes in patients with HF and diabetes treated with metformin,[30] though randomized trials in HF populations remain scarce and inconsistent as both, beneficial and neutral effects of metformin to improve myocardial metabolic and contractile efficacy have been reported.[13] A meta-analysis including 34,504 patients with HF and DM observed a 20% reduced all-cause mortality with metformin compared to other treatments.[31] A reduction of all-cause hospitalisation and hospitalisation for HF[32] with metformin treatment was reported. However, these observational data have not been confirmed in controlled clinical trials. Moreover, few data is available to address potential

underlying mechanisms of the observed mortality benefit. In one small clinical trial metformin treatment has been shown to improve functional status (NYHA class), exercise ventilator capacity (VE/VCO_2) and to decrease in BNP levels.[11] Importantly, the wide spread used of metformin was historically compromised due to the increased risk of lactacidosis, particularly in hypoxic conditions such as heart failure. However, the safety profile of metformin in HF has been reassessed in a number of studies, and concerns about lactic acidosis are no longer considered a major limitation in stable patients with preserved renal function.[33,34] In fact, metformin has evolved in this development form a contraindicated drug in HF to a safe and well established treatment option in HF.[35]

SGLT2 inhibitors have rapidly emerged as a cornerstone of heart failure therapy.[36] In the EMPEROR-Reduced,[14] EMPEROR-Preserved,[37] and DAPA-HF[27] trials, empagliflozin and dapagliflozin demonstrated consistent reductions in hospitalization and cardiovascular death, regardless of diabetes status.[38] Beyond their natriuretic and haemodynamic effects, SGLT2 inhibitors exert favourable effects on myocardial metabolism, inflammation, and mitochondrial function, and may indirectly improve insulin sensitivity. Despite the success of SGLT2 inhibitors, head-to-head comparisons with classical insulin-sensitizing agents such as metformin have not been performed.

The METRIS-HF trial is, to our knowledge, the first randomized controlled trial to compare metformin and empagliflozin in a non-diabetic heart failure population with objectively defined insulin resistance. By assessing changes in global longitudinal strain (GLS), a sensitive imaging biomarker of myocardial contractility, the trial seeks to detect early mechanistic effects of both interventions, with additional evaluation of clinical, metabolic, inflammatory, and functional outcomes. The use of GLS as the primary endpoint represents a strength of the trial, given its prognostic relevance and reproducibility in HF populations. Secondary and exploratory endpoints, including 6MWT, natriuretic peptides, QoL scores, and metabolic biomarkers, will provide a multidimensional view of therapeutic effects.

Several features of the trial design enhance its scientific and translational value: The enrichment of the study population for insulin resistance using quantitative indices (HOMA-IR); the multimodal biomarker platform, and the double-dummy blinding to mitigate bias. The inclusion of patients with both HFrEF and HFmrEF reflects current epidemiological realities and ensures broader generalizability.

Limitations include the relatively small sample size and phase II design, which preclude definitive conclusions regarding clinical endpoints such as hospitalization or mortality. However, the mechanistic focus and rigorous methodology are appropriate for hypothesis generation and signal detection, and may inform larger outcome trials.

In summary, the METRIS-HF trial will provide novel insights into the comparative effects of metformin and empagliflozin in insulin-resistant patients with heart failure. The results may support future personalized metabolic interventions and help define the role of insulin resistance as a therapeutic target in HFrEF and HFmrEF.

Conflict of Interest

See *Appendix*.

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