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Effect of intermittent fasting after ST-elevation myocardial infarction on left ventricular function: study protocol of a pilot randomised controlled trial (INTERFAST-MI)

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ABSTRACT

Introduction Preclinical studies consistently show robust disease-modifying effects of intermittent fasting in animal models of cardiovascular disease. However, the impact of intermittent fasting on cardiovascular endpoints after myocardial infarction has not been investigated in a clinical trial so far.

Methods and analysis The INTERmittent FASTing after Myocardial Infarction (INTERFAST-MI) trial is a monocentric prospective randomised controlled non-confirmatory pilot study including 48 patients with ST-segment elevation myocardial infarction. They will be randomised in a 1:1 ratio to either intermittent fasting (daily time-restricted eating; consuming food for not more than 8 hours/day, fasting for at least 16 hours/day) or to a control group without a particular diet. The follow-up time is 6 months. The prespecified primary outcome is change in left ventricular systolic function at 4 weeks from baseline to estimate effect size required to establishing sample size and power calculation for a future full-scale trial. Secondary outcomes include protocol adherence, recruitment, major adverse cardiac events, revascularisation, changes in left ventricular systolic function at 3 and 6 months, patient weight, blood pressure, and serum markers of inflammation and cardiovascular disease. Enrolment began on 1 November 2020 and is expected to conclude in December 2021.

Ethics and dissemination The trial has received ethics approval from the Medical Ethics Committee of the Martin-Luther-University Halle-Wittenberg. Results of the study will be submitted for publication in a peer-reviewed journal and presented at scientific conferences.

Trial registration number DRKS00021784.

Strengths and limitations of this study

- This is the first randomised controlled trial assessing the effect of intermittent fasting on cardiac function.
- Design of this pilot study facilitates the evaluation of feasibility and safety of the protocol and calculation of the sample size for a future multicentre trial to assess major adverse cardiac events as primary endpoints.
- Scheduling of the exact fasting periods is left up to each patient's choice, thereby improving patient's compliance and translation into clinical routine, but disguising potential effects by lack of standardisation.
- Statistical power of 60% was defined to be adequate for this non-confirmatory pilot study, but led to a small calculated sample size and might limit reliable interpretation of the results.
- Nature of the study intervention precludes any possibility of blinding.

INTRODUCTION

Long-term caloric restriction has been shown to robustly effect ageing and lifespan extension in mice and non-human primates and to exhibit numerous health-related effects in clinical trials.[1–3] It sets off an evolutionary conserved, adaptive cell response in improving the efficacy of glucose metabolism, cellular stress resistance as well as DNA repair mechanisms, and suppresses inflammatory processes. In particular, periodic flipping between fasting and non-fasting phases ('metabolic switch') improves resilience and long-term disease resistance.[2]

Preclinical animal studies illustrate the therapeutic effects of intermittent fasting, for example, in adiposity, diabetes mellitus, cardiovascular, neoplastic and neurodegenerative diseases.[4] Clinical trials provide conclusive and robust human data for the beneficial effects of fasting in adiposity, insulin resistance, dyslipidaemia, arterial hypertension and inflammation.[5] In humans, the health benefits of intermittent fasting do not seem to be solely attributed to a reduction in caloric intake. In a randomised controlled British monocentre trial, 107 overweight

women were assigned to either an intermittent fasting regime (with very low calorie diet for 2 days/week and no restriction on the other 5 days/week) or continuous reduction in daily caloric intake. Women assigned to either group lost the same amount of body weight, but those randomised to the intermittent fasting regime had a greater increase in insulin sensitivity and a larger reduction in waist circumference.[6]

Fasting improves numerous indicators of cardiovascular health including blood pressure, resting heart rate, serum levels of high-density lipoprotein (HDL), low-density lipoprotein (LDL), cholesterol, and triglycerides as well as serum levels of glucose and insulin and insulin sensitivity.[7–10] In animal studies, the improvements in cardiovascular health indicators show up at 2–4 weeks after the start of intermittent fasting. They dissipated over weeks after continuation of an ad libitum diet.[11]

These cardioprotective effects as well as the above-mentioned cellular mechanisms of intermittent fasting are crucial for myocardial healing, myocardial and vascular regeneration, as well as secondary prevention after myocardial infarction (MI).[12]

Two groups from the USA and Brazil independently investigated the effect of intermittent fasting on MI-induced myocardial remodelling in rats.[13 14] Both groups, Ahmet *et al* and Okoshi *et al* could provide robust evidence for beneficial effects of intermittent fasting in post-MI cardiac remodelling including better left ventricular (LV) function, a reduction in LV dilation and a reduction in cardiomyocyte hypertrophy. Okoshi *et al* confirmed these effects even in rats, in which intermittent fasting was initiated after MI.[14]

However, clinical trials to validate these experimental data in human disease and to finally translate it to clinical practice are still needed. We designed the INTERmittent FASTing in Myocardial Infarction (INTERFAST-MI) trial to assess feasibility of a future multicentre trial. In detail, we aim to establish sample size and power calculation required for a full-scale study. We furthermore propose to evaluate the financial, technical, administrative, and logistic feasibility, especially including issues of data collection and protocol adherence.

METHODS AND ANALYSIS

Study design

INTERFAST-MI is a prospective randomised controlled non-blinded single-centre investigator-initiated pilot trial. The study is carried out in the Department of Cardiology, Angiology and Intensive Care Medicine of the Martin-Luther-University Halle-Wittenberg. The study is sequentially conducted as follows: enrolment according to prespecified inclusion and exclusion criteria, randomisation and follow-up for 6 months with follow-up visits at 4 weeks, 3 months and 6 months, voluntary cross-over at 3 months, and assessment (figure 1). The study is designed to provide important parameters, which can be used to evaluate the feasibility and safety of the protocol and calculate the sample size for a future multicentre trial. The study protocol was designed according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trial) guideline,[15] the reporting checklist is included in the online supplemental material. INTERFAST-MI has been registered at the German Clinical Trials Register (DRKS00021784, the trial registration dataset is also included in the online supplemental material).

Study period

The study started in November 2020 and will end 6 months after recruitment of the last participant, expected in the mid of the year 2022.

Participants and eligibility

Male or female patients older than 18 years with ST-segment elevation myocardial infarction (STEMI) or equivalent are eligible for screening according to the inclusion and exclusion criteria.

Inclusion criteria

The inclusion criteria are as follows: STEMI or equivalent (ie, De Winter's sign suggesting proximal left anterior

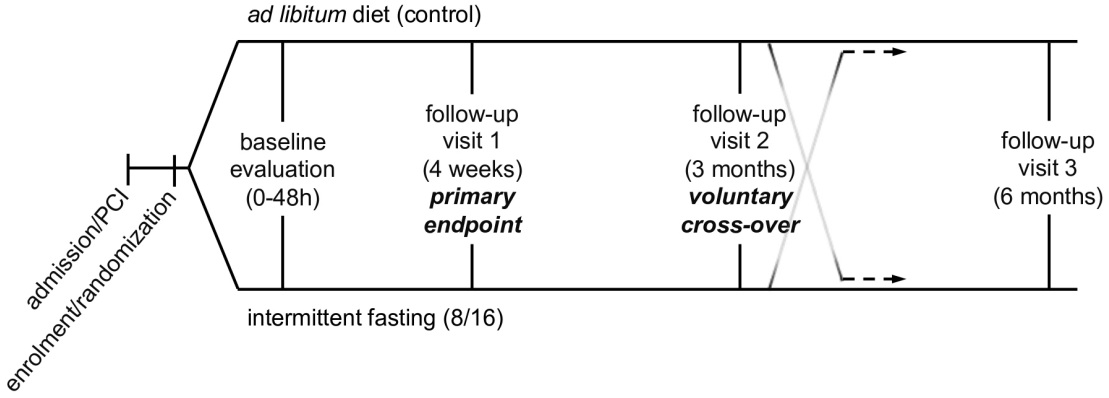

Figure 1 Study design. Following enrolment according to prespecified inclusion and exclusion criteria, randomisation and baseline evaluation are followed by visits at 4 weeks, 3 months and 6 months. At 3 months, voluntary cross-over is provided to the participants. PCI, percutaneous coronary intervention.

descending artery (LAD) lesion, new left bundle branch block (LBBB), or identification of STEMI by modified Sgarbossa's criteria in the setting of LBBB or pacemaker), written informed consent and age older than 18 years.

Exclusion criteria

Patients are excluded, if they have any of the following: concurrent participation in other interventional studies, non-MRI compliant devices, severe kidney failure (glomerular filtration rate (GFR) <30 mL/min), severe claustrophobia, antidiabetic therapy with sulfonyl urea or insulin, pregnancy, relationship of employment or other dependencies to the executing department.

Randomisation procedure and treatment allocation

Randomisation takes place within 48 hours after the revascularisation procedure. The allocation ratio is 1:1 to the study groups 'ad libitum diet' or 'intermittent fasting'. We performed blocked randomisation and generated blocks with a size of four by http://www.randomizer.org.[16] Matching for comorbidities or concurrent medication is not planned.

Study intervention

Participants randomised to the intervention arm are requested to perform intermittent fasting, that is, ad libitum diet for not more than 8 hours/day (eg, from 12:00 to 20:00) alternately with fasting for at least 16 hours/day (eg, 20:00 to 12:00) for 3 months from baseline. Scheduling of the exact fasting periods is free of each patient's choice after discharge from the hospital and can be adjusted to individual circumstances, as long as the minimum durations of the fasting periods are maintained. Intake of water and medication is allowed during fasting periods. The study arm 'ad libitum diet' is the control group without any further intervention. After 3 months from baseline, participants can cross over to the other study arm for further 3 months, if they want to, or proceed in the study arm initially randomised to.

Study outcomes

Primary outcome

The primary outcome is the change in LV systolic function as assessed by left ventricular ejection fraction (LVEF) from baseline after 4 weeks of intermittent fasting. LVEF is determined by echocardiography with the biplane Simpson's method by not more than two different physicians with expertise in echocardiography and who are blinded to treatment allocation.[17] This primary outcome has been chosen to estimate effect size required to establishing sample size and power calculation for a future full-scale trial.

Secondary outcomes

Secondary feasibility outcomes are protocol adherence and recruitment. Further secondary outcomes are death or hospitalisation due to cardiovascular events, all-cause mortality, change of LVEF from baseline after 3 and 6 months, further echocardiographic parameters (ie, wall motion, LV diastolic function and others), further MRI parameters (ie, presence of oedema, size of a myocardial scar, and others), change of body weight and blood pressure, medication, de novo diagnosis of comorbidities (especially diabetes mellitus), change of health-related quality of life (assessed by the HeartQoL questionnaire[18]), change of several laboratory parameters (ie, NT-proBNP, creatinine, fasting insulin, fasting blood glucose, HbA1c, complete blood count including white blood differential, inflammation parameters including C-reactive protein, interleukin (IL)-1, IL-6, cholesterol, LDL, HDL, triglycerides), gene expression pattern and cellular function of circulating immune cells, and DNA methylation/ageing patterns of circulating cells ('epigenetic clock').

Follow-up protocol

Within 48 hours after MI, patients are randomised and transthoracic echocardiography and cardiac MRI are performed. Cardiac biomarkers (ie, troponin, total creatine kinase and its MB isoform) are measured before starting the protocol to assess infarct injury before starting the protocol. Blood is collected at 20:00 at the day of study inclusion (pre-fasting), at 12:00 at the day after study inclusion (pre-ad libitum), and at 15:00 at the day after study inclusion (refeeding). Furthermore, comorbidities as well as medication at admission and discharge are recorded and the HeartQoL questionnaire is performed. At 4 weeks, 3 months and 6 months after inclusion, fasting blood is collected at 12:00, transthoracic echocardiography and the Heart QoL are performed, and medication as well as comorbidities are recorded. At 4 weeks, an additional cardiac MRI is performed. The complete schedule of enrolment is included in the online supplemental material.

All patients are encouraged to keep a journal and note their exact times of fasting and eating as well as once daily their body weight and blood pressure through the complete duration of the study. This journal is regularly checked by study personnel on follow-up visits. A sphygmomanometer is provided to the participants for the duration of the study.

A continuous glucose measurement (FreeStyle *Libre* 2, Abbott, Germany) to record the participant's adherence to the intervention and to compare blood glucose and nutrition profiles between the study groups is regarded as a voluntary option for the participants.

Harms

For patients undergoing intermittent fasting, severe events are conceivable only for those with diabetes mellitus treated with insulin or sulfonyl urea. These patients are thus excluded from participation. There are few side effects for a cardiac MRI, if any. Allergic reactions to the contrast agent are rare. Serious reactions in patients with renal dysfunction are reported. Patients with severe kidney failure are thus also excluded. Less severe adverse effects (ie, dizziness, falls, migraine headaches,

etc) are not explicitly tracked, but are implicated in the HeartQoL questionnaire.

Data collection and management

Patient's data collection and management is initiated after obtaining and documenting informed consent. Patient's data and samples are pseudonymised. Personal information is kept in a locked storage unit.

The data collected at baseline and follow-up visits are filled in an electronic case report form (eCRF) using the web-tool CastorEDC. Original medical records and informed consents are archived in the study centre. The data are entered independently into the database by two researchers and are checked separately by different trained researchers.

Sample size

Sample size was calculated based on published data of Bøtker *et al*,[19] the TOPCARE-AMI trial[20] and the BOOST-2 trial.[21] For the control group, we thus expected a mean LVEF of 50.6%±7% at 30 days,[19] a mean LVEF of 51.6%±10% at 4 months,[20] and a mean LVEF of 50.4%±7% at 6 months after MI.[21] A ≥5% absolute increase in LVEF was arbitrarily chosen to represent an improvement in myocardial function, that is, 55.6% at 30 days after MI.

INTERFAST-MI was designed as a non-confirmatory exploratory trial. The statistical power was thus set to 0.6 and the significance level was set to 0.05. Minimum sample size for a two-sided t-test calculated on this basis was 21 for each study group. Considering a dropout rate of 10%, we aim to randomise 24 patients to each study group.

Statistical methods

The intention-to-treat analysis set will be used as the principal analysis for efficacy analyses. All participants who have begun treatment will be included irrespective of their protocol adherence. Patients who complete at least 4 weeks of the study and comply well with the study protocol without major protocol violations will constitute the per-protocol set. The per-protocol analysis will be used as the secondary analysis for efficacy analyses. Missing data will be handled using the last observation carried forward method. Analysis of covariance will be used to analyse the change from baseline in primary and secondary outcomes adjusted for baseline values and treatment assignment. A two-tailed $p<0.05$ will be used as the cut-off for statistical significance. All statistical analyses will be performed using GraphPad Prism (V.8.4).

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting or dissemination plans of our research.

ETHICS AND DISSEMINATION

This study will be performed following the principles of the Declaration of Helsinki. All patients must provide written informed consent before undergoing any study-related procedures. The study protocol has been approved by the Medical Ethics Committee of the Martin-Luther-University Halle-Wittenberg (ref. no. 2020-118). If any significant changes must be made to the protocol, a draft of the new version will be submitted for approval. The results of the trial will be published in an appropriate journal and communicated to the academic community at scientific conferences.

DISCUSSION

INTERFAST-MI is the first randomised controlled trial investigating the effects of intermittent fasting on cardiac function after MI. It has been designed as a pilot trial to evaluate feasibility and safety of the protocol and calculation of the sample size for a future multicentre trial to assess major adverse cardiac events as primary endpoints. It has some advantages and limitations.

Intermittent fasting is the chosen fasting regime in this trial due to the additional advantages in contrast to caloric restriction. *Time-restricted eating* is the chosen type of intermittent fasting in this trial to improve the patient's adherence to the intervention. Choice of this fasting regime as well as the patient's privilege to schedule their fasting periods on their own may not only increase the patient's compliance to the study intervention but also facilitate the translation into real-world clinical practice. However, it might disguise potential effects of intermittent fasting by the lack of standardisation.

Nature of the study intervention precludes any possibility of blinding. Thus, experimental biases that arise from a participants' expectations, observer's effects on the participants, as well as observer's biases could not fully excluded. Patient's awareness of their allocation status might impact especially the assessment of the secondary outcome measure health-related quality of life.

The primary endpoint of the study is change in LVEF to establish sample size and power calculation required for a full-scale study planned to investigate the hypothesis, that intermittent fasting might improve STEMI-related heart failure. Acute MI might cover up undiagnosed pre-existing heart failure with reduced ejection fraction (HFrEF). Patients with already diagnosed HFrEF might experience STEMI-related worsening of their cardiac function as other patients do and are hypothesised to benefit from intermittent fasting in a similar way. Incident diagnosis of HFrEF has thus not been included in the secondary outcomes and exclusion criteria and change in LVEF was chosen instead of arithmetic mean or median LVEF values. However, subanalyses of patient groups with certain LVEF margins (eg, <40%, 40%–50%, >50%) could be useful for the design of a future large trial.

Finally, a statistical power of 60% was assumed to be sufficient to evaluate protocol feasibility and safety of this non-confirmatory trial and to allow study conduction in an accessible manner. Nevertheless, it led to a small

calculated sample size and might limit reliable interpretation of the results.

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