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Study Protocol

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An **O**pen, **P**rospective study on the **E**fficacy of i**R**on therapy using intravenous (IV) iron supplements relative to oral iron intake for increasing left ventricul**A**r systolic function in patients with **M**yocardial **I**nfarction **(OPERA-MI).**

Introduction

Important cellular processes depend on iron and homeostasis of iron is well regulated. Furthermore, iron is essential for oxygen transport and storage, cardiac and skeletal muscle metabolism, energy production in the mitochondria, synthesis and degradation of proteins, lipids and ribonucleic acid, the correct functioning of immune and nervous systems [1]. Iron causes a protective effect in myocytes during hypoxia. Iron deficiency (ID) is more detrimental for the vitality of cardiomyocytes and skeletal myocytes during hypoxia, compared to iron excess [2]. ID directly affects function of the heart and leads to mitochondrial disfunction and adversely affects cardiomyocyte contractility and relaxation [3]. ID has been shown to be an independent predictor of poor outcomes, irrespective of the presence of anaemia, in patients with heart failure (HF) [4-9].

Negative impact of ID on the left ventricular (LV) function, quality of life and outcomes in patient with acute coronary syndrome (ACS) has been shown [10-14]. However, the effects of ID treatment in patient with myocardial infarction (MI) has not been well studied.

Methods

Proposed study uses an open-label prospective randomized single-center study approach. 360 patients, with or without ID, hospitalized with MI are recruited at the Kazan city clinical hospital №7, which is the clinical base of Kazan State medical university. Patients with ID (n=240) are randomised (1:1) to either intravenous (i.v.) FCM or oral ferrous sulphate. Patients with normal iron status (n=120) are in the control group.

The trial, which is conducted in strict compliance with Good Clinical Practice (GCP) and with the Declaration of Helsinki, was approved by the Local Ethics Committee.

Study population. Male and female patients aged ≥18 years, hospitalised with MI and diagnosed according to **Fourth Universal Definition of MI and Myocardial Injury (ESC 2018), with** hypokinesia or akinesia in at least two connected LV segments according to echocardiography results obtained within the first 24 hours after myocardial infarction occurs, will be considered for participation. All patients who agreed to participate will be asked to provide written informed consent before any trial-related procedure is performed.

Inclusion and exclusion criteria. Inclusion/exclusion criteria are shown in Table 1

Definition of MI. MI is diagnosed according to **Fourth Universal Definition of MI and Myocardial Injury (ESC 2018)** when there is a rise and/or fall of cardiac troponin values (cTn) values with at least one value above the 99th percentile upper reference limit (URL) and at least one of the following signs: symptoms of myocardial ischaemia, new ischaemic ECG changes, development of pathological Q waves, imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology [15].

Definition of ID. ID is defined as serum ferritin <100 ng/mL (absolute ID) or 100 ng/mL ≤ serum ferritin ≤299 ng/mL if transferrin saturation (TSAT) <20% (functional ID) [9].

Assessment of LV systolic function. LV systolic function is assessed by transthoracic echocardiography with evaluation of Wall motion score index (WMSI) using 16-segment model [16].

Assessment of quality of life. Quality of life is assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ) [17]

Screening. During screening all risks and benefits of participation are described to each patient who fit the chosen inclusion criteria. Each patient considered in the study will be provided 2 copies of written consent and will receive one copy of the consent, in addition each patient will receive a form containing information about study participation. Anamnesis, physical examination, echocardiography, KCCQ, complete blood count (CBC), serum iron level, total iron binding capacity (TIBC), serum ferritin level, TSAT, alanine transaminase, aspartate transaminase, creatinine are performed at the screening visit within 24 hours after MI. The data of each study participant will bes entered into individual patient registration cards specially designed for each visit.

Randomisation and study treatment dosing regimen. Patients with ID are randomised to either i.v. FCM or oral ferrous sulphate randomly with block randomizations. The FCM doses were determined using the patient's screening visit body weight measurement and haemoglobin value (table 2). Patients receives all doses during hospitalization accordance with the drug local

labels. 100 mg of ferrous sulphate is administrated 2 times per day during hospitalization and continue within next 2 month.

Study outcomes. The primary significant outcome is the decrease in WMSI value. The secondary outcome the composite of cardio-vascular (CV) mortality, non-fatal stroke, non-fatal MI, recurrent HF hospitalizations.

Patient Assessments. All participants are observed for 12 months from the first visit after the admission to the study. Participants are evaluated in-person at 3-, 6-, and 12-month intervals with correction of treatment if necessary. Participants are also evaluated monthly through telephone consultation. Echocardiography with WMSI evaluation, KCCQ, CBC, serum iron level, TIBC, serum ferritin level, TSAT is perfumed during every physical evaluation visit. Primary and secondary outcomes are established during follow up period.

Statistical analysis. Statistical data is analysed using standard methods of descriptive statistics. For categorical variables, summary tabulations of the number and percentage of subjects within each category of the corresponding parameterwill be presented. For continuous variables, the mean, median, standard deviation, first and third quartiles, and minimum and maximum values will be presented. Clinical-laboratory associations will be assessed as well as associations with outcomes (Kaplan-Meier subgroup survival curves). The level of significance to be used for tests will be 0.05.