SUMMARY

EudraCT No	2018-001057-26
Project title	Management of the patient with heart failure and diabetes: may insulin be a problem? A pilot randomized clinical study
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Rationale and Objective	Cardiac failure (HF) and type 2 diabetes mellitus (T2DM) are two clinical conditions with a significant impact on public health worldwide. In the elderly population the prevalence of T2DM is constantly increasing as well as its incidence in all Western countries including Italy. The combination of HF and T2DM is frequent and leads to an increased risk of death and of non-fatal adverse cardiovascular (CV) events which justifies the frailty of this population. Although diabetic patients (pts) with HF respond to recommended treatments for HF, the effective and safe control of blood glucose levels is still an outstanding clinical problem, since glucose lowering drugs may increase the risk of CV adverse events. Insulin, used in about 30% of diabetic patients with HF, causes adverse effects such as fluid and sodium retention and unwanted effects of hypoglycemia. Even if insulin remains a milestone in glucose lowering therapy of T2DM, its risk/benefit ratio is still controversial, more so when given to old patients with HF. The issue has gained relevance since new antidiabetic agents, as the sodium glucose co-transporter 2 (SGLT-2) inhibitors and glucagon-like peptide (GLP-1) analogues, with a safer CV profile have been made available. While the transferability of the CV benefits attributed to the new drugs needs to be assessed in clinical practice, the present study explore the benefit/risk profile of insulin in HF. Objectives: to assess comparatively in patients with heart failure and T2DM the benefit/risk profile over 1-year follow-up of two antidiabetic strategies, standard care with vs without insulin in terms of humoral and clinical endpoints including body weight change, all-cause mortality and burden of care components (hospitalizations for CV events and episodes of severe hypoglycemia).
Trial design and population; statistical aspects	**Study Population** **Inclusion criteria:** • men and women aged ≥70 years; • at discharge after admission to hospital for worsening of HF or ambulatory patients with chronic HF; • New York Heart Association (NYHA) class II or III • with any level of left ventricular ejection fraction;

	• plasma natriuretic peptide (BNP) ≥200 pg/mL or N-terminal pro-BNP ≥900 pg/mL (NT pro-BNP) • prior history or newly diagnosed T2DM; • candidate by the responsible physician to insulin therapy; • signed informed consent. **Exclusion criteria:** • significant renal insufficiency (GFR <30 mL/min/1.73 m^2) or severe liver disease (liver function test abnormalities (alanine or aspartate aminotransferase ≥ 3 × upper limit of normal [ULN]); • levels of hemoglobin <10 g/dl; • HbA1c ≤5% or ≥11%; • unstable diabetes*:* type of diabetes presentation in patients with an anamnesis of frequent episodes of hypoglycemia, hyperglycemic hyperosmolar state, ketoacidosis or lactic acidosis*;* • planned CV surgery or angioplasty in 3 months; • any non-cardiac disease that shortens life expectancy to<1 year (e.g. most cancers); • inability to comply with study protocol; • participation to another interventional clinical study.
Trial design and population; statistical aspects	**Trial design:** randomized, open-label, controlled, multicenter, PROBE design (Prospective Randomized Open Trial with Blinded Evaluation of Outcomes), and central adjudication of adverse events. The primary endpoint, glucose variability, will be computed from 3 daily glucose profiles (each with at least 5 self-measurements of blood glucose) performed before the baseline, 1, 6, 12 months follow up and end study visits and calculated as the average of the three daily standard deviations. Blood glucose values will be reported by the patient in an ad hoc form and the responsible physician will input this data in the e-CRF. An intensive ambulatory self-monitoring of weekly body weight and possible changes in diuretic treatment is required. Patients will be provided with ad hoc forms for data collection. At 1, 6, 12 months of follow up and/or at end of study visit: a) patients will be examined, b) the information about clinical events will be collected. c) natriuretic peptide plasma concentration, HbA1c and urinary albumin excretion will be measured Echocardiographic evaluation will be done at baseline, 1 and 12 months after randomization.

	Central randomization: Central randomization in a 1:1 ratio will be performed by a web-based system. The system will ask to confirm all inclusion and exclusion criteria. A patient will be considered randomized when the randomization system will assign the treatment arm (standard care with insulin or standard care without insulin) and patient's identification number according to a pre-established randomization list. Randomization will be stratified by Center. **Study Endpoints** **Primary endpoint:** The main endpoint of this pilot study is to assess in patients with heart failure and T2DM whether an anti-diabetic strategy of standard care without insulin decreases glucose variability compared to a strategy of standard care which includes insulin. **Secondary endpoints:** The effects of the two antidiabetic strategies will be also evaluated in terms of the following safety and efficacy markers: • incidence of documented hypoglycemic episodes; • body weight; • natriuretic peptide; • urinary albumin excretion; • NYHA class • hospitalizations for HF and for any cause; • CV and non-CV mortality; • episodes of ketoacidosis/lactic acidosis; • LVEF and E/e' by echocardiography; • HbA1c. **Sample size:** Given the complexity of the problem, the absence of similar published studies and the need to enroll a large number of patients to obtain a definitive answer, the present study will be explorative by nature. Assuming an effect size of 0.5 (i.e. half standard deviation difference between groups) we calculated that 142 patients (71 per group) will be required for the study, with an alpha of 0.05, a power of 80% and a 10% drop-out rate.
Safety	Severe adverse events possibly attributable to insulin treatment will be specifically monitored and sent to the Coordinating Center within 24 hours. The presence of other adverse events will also be carefully checked for at the scheduled follow-up visits.
Data safety and monitoring board	An independent Data Safety Monitoring Board (DSMB) will monitor the safety and overall evolution of the study.

Time scale	**Randomization:** Start: September 2018 End: September 2019 **Follow-up** Start: September 2018 End: October 2020 **Study duration:** The expected duration of the study for each subject is 12 months, for a total study duration of 2 years, considering 12 months for patient inclusion.