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DEPARTMENT OF CARDIOVASCULAR RESEARCH

Area: Assessment of impact of interventions aimed at improving safety and quality of care.

Management of the patient with heart failure and diabetes: may insulin be a problem?

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ABSTRACT

Relevance of the project: cardiac failure (HF) and type 2 diabetes mellitus (T2DM) are two diseases with a significant impact on public health worldwide. In particular, 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. Although diabetic patients with HF respond to recommended treatments for HF, the effective and safe control of blood glucose levels is still an outstanding clinical problem, since hypoglycemic drugs may increase the risk of CV adverse events. Recent large scale clinical trials have shown that a sodium-glucose cotransporter 2 (SGLT-2)-inhibitor, empaglifozin, and analogues of glucagon-like peptide (GLP-1), liraglutide and semaglutide, were safe and may even decrease the risk of hospitalization for HF and of cardiovascular death in patients with diabetes and HF. It is therefore necessary to compare in these patients the efficacy and tolerability of these novel drugs with traditional hypoglycemic agents including insulin. Insulin, used in about 30% of diabetic patients with HF, causes adverse effects such as fluid and sodium retention and severe hypoglycemia which can be particularly harmful to the patients with HF. These patients are more prone to fluid retention and to unwanted effects of hypoglycemia such as lethal arrhythmias and decrease in myocardial contractility. Several studies have suggested an association between insulin and worse outcomes in HF, independent of the severity of the disease.

Objectives and design: even if insulin remains a milestone in hypoglycemic therapy of T2DM, its risk/benefit ratio needs to be assessed, in fragile patients such as the elderly with HF. The availability of new hypoglycemic drugs which for the first time may decrease the CV risk by reducing mortality and hospitalizations for HF, is a unique opportunity to compare the effects of insulin with those of old and new hypoglycemic drugs on

1. incidence of serious hypoglycemic episodes, the variability of blood glucose levels and the increase in body weight (primary endpoint);
2. severity of HF, the hospitalizations for HF and for any cause, and CV and non-CV mortality according to different therapeutic strategies;
3. plasma levels of NT-proBNP and urine albumin (microalbuminuria).

Considering the complexity of the problem and the need for large number of patients necessary for a definitive clinical trial, the present study will be exploratory in approximately 200 patients, so that its results will be the base for future large scale clinical trials.

BACKGROUND AND RATIONALE

Heart failure (HF) is a disease of high impact on Public Health, not only for its high prevalence, approximately 420 million people affected worldwide, but also for the increasing incidence attributable to the increase of the mean age of the population (Ambrosy, 2014). HF is the most frequent cause of hospitalization and disability in people aged 65 or over (Christiansen 2017) with a 5-year mortality comparable to that of patients with the most frequent cancers (Stewart 2010). Prevalence and incidence of some risk factors for this disease are changing in the last years, such as type 2 diabetes mellitus (T2DM) (Mozaffarian 2016). In Italy about 3 million people have diabetes, prevalence of this disease is constantly increasing, from 3.9% in 2001 to 5.4% in 2012 (*http://www.istat.it/it/files/2012/09/Il-diabete-in-Italia.pdf*), in particular in Lombardy prevalence increased by 40%, from 3% in 2000 to 4.2% in 2007. The prevalence of diabetes is much higher in the elderly population: nationwide it is 15.2% in subjects aged 65 to 74 years, and 20.3% in those of 75 years or older (www.ibdo.it/pdf/Diabetes-Report-2014.pdf). Diabetes is a chronic disease associated to an elevated morbidity and mortality, mainly cardiovascular (Roger 2012, Baviera 2016). After peripheral artery disease, HF is the most relevant comorbidity of T2DM (Shah 2015). Both T2DM and pre-diabetes double the risk of death in HF, when compared to HF without diabetes (Pocock 2006; Barlera 2013, De Groote 2004), and even if patients with diabetes respond to recommended therapy of HF, glycemic control is still a controversial clinical issue (Gilbert and Krum 2015). Moreover, the relation between glycemic control and incidence of complications is complex: observational and interventional studies showed that glycemic control may improve microvascular complications, but not much macrovascular complications, with no effect on mortality (Rossi 2015). In other words, to date there are no antidiabetic therapies devoid of risks of fluid retention, of glycemic variability and of severe hypoglycemia (triad) (Palmer 2016, Stratton 2000).

Metformin is considered first choice hypoglycemic agent in patients with HF, according to guidelines; it is contraindicated in case of severe renal or liver dysfunction (Eurich 2013, Palmer 2016). Recent large scale clinical trials showed that a sodium-glucose cotransporter 2 (SGLT-2)-inhibitor, empaglifozin, and analogues of glucagon-like peptide (GLP-1), liraglutide and semaglutide, were safe and may even decrease the risk of hospitalization for HF and of cardiovascular death in patients with diabetes and HF (Zinman 2015; Marso 2016; Marso 2016; Fitchett 2016).

Therefore, cardiovascular effects of these new hypoglycemic agents should be evaluated specifically in diabetic patients with HF, with special focus on insulin (Eurich 2008; Gilbert and Krum 2015; Hippiseley-Cox & Coupland 2016), a drug used since a long time in at least 30% of patients with diabetes (Inzucchi 2015; Garber 2016), but it causes, as all drugs, adverse reactions such as sodium and fluid retention, severe hypoglycemic episodes which can worsen the already depressed cardiac function of a patient with HF (Fisher 1990). Another consequence of severe hypoglycemia may be lethal arrhythmias (Hanefeld 2016). Studies results suggest that the increased risk of increased morbidity/mortality associated to insulin may be attributable a prescription bias (e.g. insulin is prescribed to patients with longer lasting diabetes, more

severely ill) (Gilbert and Krum 2015; Eurich 2008; Gilbert and Krum 2015; Hippiseley-Cox and Coupland 2016), rather than to insulin per se.

The studies mentioned above on liraglutide and semaglutide deserve special interest. In these studies, the fraction of patients on insulin at baseline was similar in both study groups, while incidence of new prescriptions of insulin were at least two times lower in active treatment than in placebo group (Table; Cosmi 2017). This suggest that liraglutide and semaglutide may reduce the need for insulin in patients with diabetes and HF, a particularly fragile population.

Insulin prescription rate (% of patients) at entry and started during study by treatment arm in the SUSTAIN-6 and LEADER trials.

	At entry		**Started during study**	
	Active treatment	Placebo	Active treatment	Placebo
LIRAGLUTIDE	43.7	45.6	28.8	43.2
SEMAGLUTIDE 0.5 mg/die	58.0	58.0	10.3	24.8
SEMAGLUTIDE 1.0 mg/die	58.0	58.1	8.5	23.2

Despite its importance, the benefit/risk ratio of insulin is not well known, particularly in fragile elderly with HF. Indeed, this ratio has never been evaluated in a prospective study, due to intrinsic limitations: it would not be ethical to randomize patients to receive insulin or placebo.

Thus, the aims of the present proposal will be to assess, in elderly patients with chronic HF and diabetes:

a) the rate of severe hypoglycemic events, glycemic variability and body weight increase (Triade) in patients treated with oral hypoglycemic agents only, insulin alone or combined with oral hypoglycemic agents, or with empaglifozin/liraglutide (primary endpoint);
b) HF severity, admission to hospital for HF or for any cause, cardiovascular and non-cardiovascular mortality;
c) plasma concentration of NT-proBNP and urinary albumin excretion (microalbuminuria) in the treatment arms.

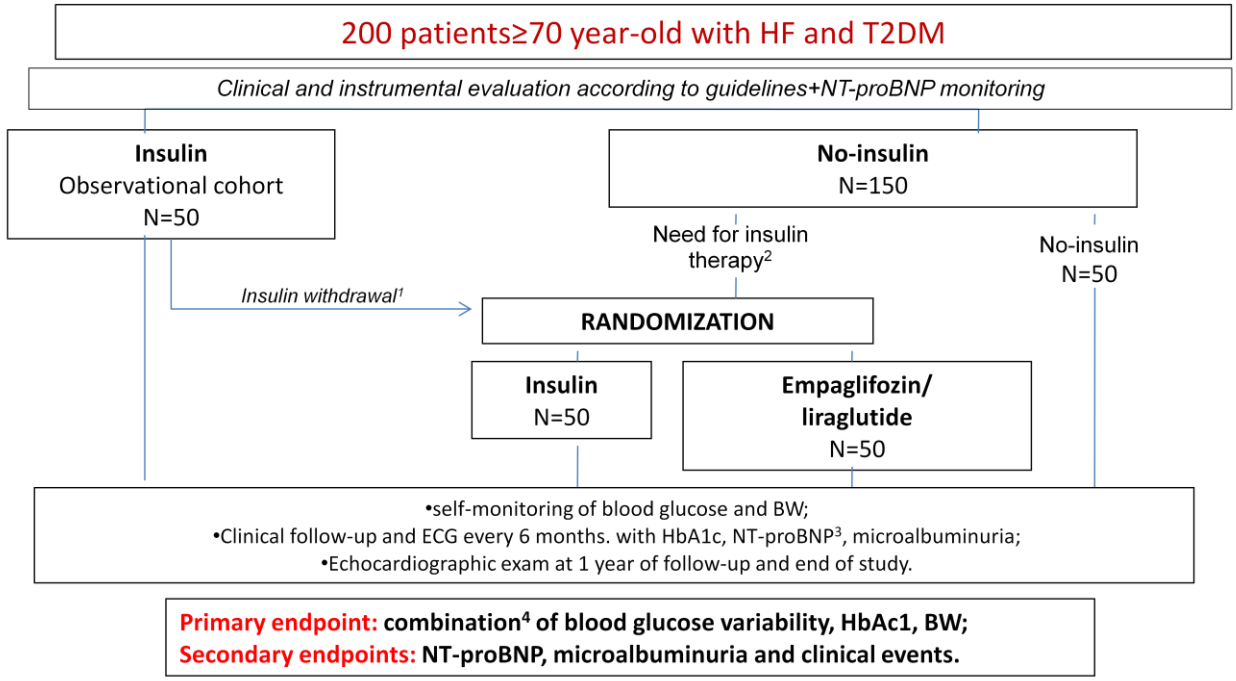
Given the complexity of the problem and the need for a large number of patients to be enrolled in a definitive study, the present proposal is exploratory by nature and will be the premise for designing a larger study.

PATIENTS AND METHODS

The study will enroll 200 diabetic patients with chronic HF of any cause, aged 70 years and older, identified in 3 cardiology wards of the Lombardy region (Treviglio, Passirana di Rho and Desio); they will be divided into 3 groups, according to their characteristics (see study flow-chart):

1) *patients on insulin* (n=50): patients already on treatment with insulin alone or in association with other antidiabetic agents.
2) *patients not receiving insulin* (n=150):
    a. patients who will never need insulin during follow-up (n=50);
    b. patients who will need to be started on insulin during follow-up, will be randomly assigned to either (a) insulin (n=50), or (b) emapglifozin or liraglutide (n=50). This subgroup of patients will be made also of those already on insulin (group 1) who will accept to stop insulin and to be assigned randomly to either insulin or emapglifozin or liraglutide. By this way we'll make sure that a sufficient number of patients will be present in group 2.b.

Study flow-chart



1: *pts will be identified according to (1) clinical criteria for a safe withdrawal, (2) informed consent of the individual pt, (3) number of pts needed;*
2: expected incidence should be >=5%/year, according to administrative data (Regione Puglia) and to trial data (SUSTAIN-6, LEADER trials);
3: NT-proBNP measured in local clinical chemistry laboratories;
4: details on construction of primary endpoint will be provided in the study protocol.

Inclusion criteria

- Diagnosis of heart failure, with any level of left ventricular ejection fraction;
- Type 2 diabetes mellitus, treated with hypoglycemic drugs;
- Age>=70 years;
- Possibility to control blood glucose and body weight either by the individual patient or by a care-giver;
- Signed informed consent.

Exclusion criteria

- Life expectancy <2 years;
- Unavailability to attend follow-up visits
- Participation to another clinical study.

Time line of different exams are reported in the Table.

Exams	**Study entry**	**6-month follow-up**	**12-month follow-up**	**End of study**
Signed Informed consent	√	-	-	-
Clinical exam	√	√	√	√
Endpoints	√	√	√	√
Echocardiogram	√	-	√	√
Blood chemistry (including blood cell count, urea, creatinine, electrolytes, blood glucose*, HbAc1, total and HDL cholesterol, LDL, liver enzymes, NT-proBNP)	√	√	√	√
Urine exams	√	√	√	√
Microalbuminuria	√	√	√	√
Blood pressure*	√	√	√	√
Heart rate*	√	√	√	√
Body weight*	√	√	√	√
Adverse events and SUSARs	√	√	√	√
*: these controls should be done by the individual patient and recorded in ad hoc forms to be given to the physician during the follow-up visit.				

Notes

- Daily self monitoring of post-prandial (2 h) blood glucose with POC distributed by NHS;
- Weekly self-monitoring of arterial blood pressure, heart rate and body weight;
- Every patient will be informed with ad hoc brochures on signs and symptoms relative to their disease(s) requiring direct contact with the attending physician.

STUDY ENDPOINTS

Primary end-point

- *Incidence of hypoglycemia*, symptomatic or not (blood glucose <70 mg/dL);
- *Glycemic variability*: incidence and extent of fluctuations around the mean of glycemic values. Reference values: post-prandial glycemia<160 mg/dL; standard deviation <40 mg/dL of at least 2 daily measurements over 14 days in one month (De Micheli 2007).
- *Body weight increase*: >=2 kg increase in less than 7 days. Body weight will be monitored daily during the study, to assess changes over time. Possible changes in diuretic and hypoglycemic therapy will be recorded.

Secondary endpoints

- *All-cause mortality*
- *Cardiovascular and non-cardiovascular mortality*
- *Hospitalizations for cardiovascular reasons;*
- *Hospitalizations for worsening of heart failure;*
- *Acute myocardial infarction or other acute coronary syndrome;*
- *Stroke;*
- *Amputations.*

HbA1C and NT-proBNP will be assayed in clinical chemistry laboratories at the participating centers. *Urine albumin* will be assayed in a central laboratory on freshly collected spot urine. All documents relative to endpoint events should be sent to the Scientific Secretariat at IRCCS Mario Negri Institute, Milano, to be validated by an independent Event Validation Committee.

Randomization: web-based randomization will be performed; both the randomization system and the web-based CRF will be created and managed by IRCCS Mario Negri Institute, Milano.

Data collection, database and study center monitoring

Individual data will be collected by each investigator and input online in an electronic case report form (eCRF). The input data will be available in real time for inspection and monitoring by the Scientific Secretariat of the study. Data management will be under the responsibility of the Department of Cardiovascular Research of the IRCCS – Mario Negri Institute for Pharmacological Research in Milan. The clinical centers and clinical data will be monitored by a certified clinical monitor.

INNOVATIVE ASPECTS AND RELEVANCE OF THE PROPOSAL

The main originality of the proposal is the prospective evaluation of mechanisms that are involved in the possible worsening of heart failure in patients treated with insulin compared to a) traditional oral hypoglycemic agents and b) new hypoglycemic agents such as empaglifozin/liraglutide. The rationale of the proposal lies in the results of a study currently ongoing at the Mario Negri Institute that can be summarized as follows:

- in an analysis of administrative data from the Puglia region done on 103,857 diabetic subjects identified in 2008, 33,643 (32.4%) of them had also heart failure. In these patients, insulin therapy, alone or in combination with other hypoglycemic agents, was associated with a significant increase in the 5-year risk of death and re-hospitalization (OR [95%CI]= 2.73 [2.55-2.92] and 1.68 [1.57-1.80], respectively).
- a meta-analysis of 4 large clinical trials in heart failure shows an increase mortality attributable to insulin.

Only a prospective study will allow to collect in a homogenous and reliable way the clinical ad therapeutic characteristics, as well as data related to history and time of onset of diabetes and heart failure. All the risk factors for mortality and morbidity, and the intercurrent events that were identified in previous retrospective studies will be accounted for in a more comprehensive and rationale way. 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 and will help in designing subsequent larger studies.

TIMELINE OF THE PROPOSAL

		Time frame*
Final protocol & documents/Approval by Ethics Committee		01/09/2017 – 28/02/2018
Patients enrollment	Start	01/03/2018 – 28/02/2019
	End	
End of follow-up		28/02/2020
Clinical centers closure, analysis and data presentation		01/03/2020 – 31/08/2020
Total duration of the proposal		3 years
* timeline based on a possible approval of the proposal by Fondazione Casiraghi on 01/09/2017		

After final drafting of the protocol and preparation of the web-based case report forms (eCRF), the study after the approval by competent Ethics Committees will be initiated in each Clinical Center.

BUDGET

	Description	***Cost (euro)***
Communication	Phone calls to centers, help-line	2.500
Statistical analysis and data management	-	6.500
Clinical monitoring	3 visits/center, 3 centers	6.100
Investigators' meeting	3 meetings: kick-off, after 1 year, final results presentation	1.500
Insurance	Clinical trial insurance	10.000
Publication fees	Open-access publication	2.000
Coordination personnel Research fellows	Senior scientist, 10% Fellow, trial coordinator (15000/center)	10.500 45.000
Overhead	Calculated after exclusion of fees for fellows	5.865
Total		**89.965**

Budget split-up by year	**1st year**	**2nd year**	**3rd year**	**Total**
Communication	1500	500	500	2.500
Statistical analysis and data management	2000	1500	3000	6.500
Clinical monitoring	2000	2000	2100	6.100
Investigators' meeting	500	500	500	1.500
Insurance	3333	3333	3333	10.000
Publication fees			2000	2.000
Coordination personnel Research fellows	3.500 15.000	3.500 15.000	3.500 15.000	10.500 45.000
Overhead	1925	1700	2240	5865
Total	**29.758**	**28.033**	**32.173**	**89.965**

AGREEMENTS FOR COLLABORATION WITH OTHER PUBLIC ITALIAN ORGANIZATIONS

Agreements will be subscribed with the Administration (ASST) of the 3 Clinical Centers participating to the proposal to cover the cost of a research fellow in each center (15.000 Euro each):

- UOC Cardiologia, Ospedale di Treviglio,
- UOC Cardiologia Riabilitativa, Presidio Ospedaliero di Passirana, Rho,
- Presidio Ospedaliero di Desio, SC di Cardiologia-Utic.

The new investigative drugs will be supplied in kind to the clinical centers by the pharmaceutical companies that commercialize these drugs. Therapies and instrumental exams are all parts of the expenses normally covered by the national health system.

COLLABORATIONS WITH PRIVATE ORGANIZATIONS OR COMPANIES

Not applicable.

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