METFORMIN CONTINUATION SAFETY IN DIABETIC PATIENTS UNDERGOING CORONARY ANGIOGRAPHY: THE NO-STOP STUDY

PROTOCOL

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1 PROTOCOL SYNOPSIS

Study title	Metformi**n** c**o**ntinuation **s**afe**t**y in diabetic patients undergoing c**o**ronary angiogra**p**hy.
Acronym	NO-STOP
IRCCS internal sites:	Cardio Center, IRCCS Istituto Clinico Humanitas – Via Manzoni 56, Rozzano (MI)
IRCCS external sites:	None
Population	Diabetic patients treated with metformin undergoing coronary angiography.
Objectives	To assess the safety of metformin in diabetic patients undergoing coronary angiography in terms of risk of lactic acidosis. Individuate eventual clinical, echocardiographic predictors of lactic acidosis in this setting.
Study design	Prospective, no-profit, single arm trial, powered for non-inferiority with respect to historical cohort.
Sample size	The study require the enrollment of at least 110 patients.
Primary endpoint	Increase of 20% from preprocedural lactic acid values.
Secondary endpoints	Contrast-associated acute kidney injury after coronary angiography. Lactic acidosis development after coronary angiography. Correlation between clinical, laboratoristic, and echocardiographic variables and lactic acid values.
Inclusion criteria	Diabetic patients treated with metformin undergoing coronary angiography.
Exclusion criteria	Known coronary anatomy with planned complex percutaneous coronary intervention with high probability of large amount of contrast use (>150 ml). Moderate to severe impairment of renal function (eGFR<45 ml/min). Moderate to severe impairment of liver function (Child-Pugh class B or C). Severely impaired left ventricular ejection fraction (LVEF <35%). Patients undergoing primary percutaneous coronary intervention (i.e., patients presenting with ST elevation myocardial infarction). Severe to very severe chronic obstructive pulmonary disease (GOLD class 3 to 4). Patients scheduled for cardiac surgery in the following 5 days. Inability to provide informed consent.
Prespecified subgroup analyses	Patients taking other antiglycaemic drugs on top of metformin. Patients requiring percutaneous coronary angioplasty. Patients with mild and moderate renal function impairment (eGFR<90 and <60 ml/min). Patients undergoing urgent coronary angiography (<24 hours from the index event).
Follow-up	The days after coronary angiography, at discharge and after three days from coronary angiography.

1.1. TIME SCHEDULE

Event	Screening	Post-procedure	At discharge	At three days
Type of contact with the patient	Visit		Visit	Visit/phone call
Inclusion/exclusion criteria	X			
Informed consent	X			
Medical hystory	X			
Physical examination	X	X	X	
Hemocrome, kidney and liver function, lactic acid	X	X	X	X
CK-MB, hs-troponin I, BNP	X	X	X	
Transthoracic echocardiography	X			
12-leads electrocardiogram	X	X	X	
Lactic acidosis, death, kidney failure, liver failure		X	X	X

2. BACKGROUND

Metformin is an antiglycemic drug member of biguanide class, firstly introduced in 1957 for the treatment of non-insulin dependent diabetes mellitus. It is the most widely prescribed drug for glycemic control in diabetic patients and it is often used in combination with other antiglycemic drug and insulin.[1,2] Its mechanism of action depends on decreased hepatic gluconeogenesis and glycogenolysis,[3] and increased skeletal muscle glucose uptake.[4] Moreover, metformin is also associated with a reduction in cardiovascular morbidity and mortality, when compared to insulin or sulfonylureas.[5] Diabetes mellitus is extremely common among patients with coronary artery disease, with prevalence reaching 40% in some reports of patients undergoing percutaneous coronary intervention.[6] Therefore, metformin is one of the most common drug prescribed to patients with indication for coronary angiography. Notwithstanding, the biguanide agent that preceded metformin, phenformin, was withdrawn from clinical practice in 1978, due to an unacceptable risk of lactic acidosis, ranging from 40 to 64 cases per 100,000 patient-years.[7] However, metformin present different pharmacokinetics and pharmacodynamics properties, with an estimated risk of lactic acidosis ten to twenty times less than that of phenformin. Considering the high risk of lactic acidosis with its predecessor phenformin and the high mortality of this condition, the vast majority of physician used to suspend metformin before contrast use.[8]

The incidence of lactic acidosis after metformin has recently come into question, while it has been recognized that the routinely discontinuation of metformin could carry the converse risk of deleterious effects on glycemic control, increased cardiovascular and acute kidney injury risk.[9] Metformin itself is not directly nephrotoxic,[10] but in patients predisposed to acute deterioration in renal function after contrast administration, i.e., contrast-induced nephropathy (CIN), it has been postulated that there is the potential for metformin to accumulate, leading to lactic acidosis. However, evidence for this is totally lacking.[8,11] Firstly, although CIN occurs in 2% to 25% of patients undergoing coronary intervention,[12] not every patient on metformin that develops CIN develops lactic acidosis.[13] Secondly, most of the reported cases of lactic acidosis in patients taking metformin have been in patients with severe underlying conditions, including renal dysfunction, septicemia, hepatic failure and acute left ventricular failure, any of which could in themselves contribute to the lactic acidosis.[14–16]

3. POTENTIAL RISKS AND BENEFITS

The present study aims to evaluate the strict application of the 2018 European Society of Cardiology on myocardial revascularization, that recommends to check renal function if patients have taken metformin immediately before angiography and withhold metformin if renal function deteriorates.[11]

A recent meta-analysis, using pooled data from 347 prospective comparative trials and observational cohort studies, found no cases of fatal or non-fatal lactic acidosis in 70,490 patient-years of metformin use nor in 55,451 patient-years in the non-metformin group.[17] Using Poisson statistics with 95% confidence interval the authors reported that the upper limit for the incidence of lactic acidosis in patients taking metformin was 4.3 cases per 100,000 patient-years, and in the non-metformin group the upper limit for the incidence of lactic acidosis was 5.4 cases per 100,000 patient-years. The risk for acute kidney injury in patients undergoing angiographic procedure with those preventive measures constantly applied in our center is considered to be the same of those patients not undergoing procedure without iodinated contrast medium. Moreover, we will

exclude from the study all those patients considered at augmented risk of CIN.[10,12] Therefore, we assume that the risk for lactic acidosis in our expected population is the same that patients have with their everyday metformin assumption.

Moreover, considering the documented augmented risk of hyperglycemia in patients suspending metformin for angiographic procedure,[8] and the augmented risk of serious adverse events in patients with hyperglycemia,[18] there could be the advantage of maintaining the usual antiglicemic therapy including metforminthat should be probably more appropriate than an empiric insulin regimen started at hospital admission.

4. STUDY OBJECTIVES

Assess the safety of metformin in diabetic patients undergoing coronary angiography in terms of risk of lactic acidosis. Individuate eventual clinical, echocardiographic predictors of augmented lactic acid after coronary angiography.

5. STUDY DESIGN

The study is designed as a prospective, observational, single arm study.

Enrollment timing: enrollment rate will determine the duration of the study. We estimate that one year will be sufficient to achieve this objective.

Enrollment center: the study will be conducted at the Cardiac Center of the Humanitas Research Hospital, via Manzoni 56, Rozzano (MI).

7. ENDPOINTS

7.1. Primary endpoint

An increase of lactic acid of 20% from preprocedural values in patients undergoing coronary angiography without discontinuing metformin.

7.2 Secondary endpoints

Contrast-associated acute kidney injury after coronary angiography.

Lactic acidosis development after coronary angiography.

Correlation between clinical, laboratoristic, and echocardiographic variables and lactic acid values.

8. STUDY POPULATION

8.1. Sample size

In our historical cohort of diabetic patients taking metformin, we observed a mean value of lactic acid of 1.2+0.7 mmol/l.

A total of 106 patients in an estimated time of one years are planned to be enrolled in order to detect with 90% power a prespecified increase of lactic acid of 20% from preprocedural values with a probability of alpha error of

0.05.

8.2. Patients' features

All diabetic patients undergoing coronary angiography will be screened for the enrollment in the present study.

Inclusion criteria:

We will include diabetic patients treated with metformin undergoing coronary angiography.

Exclusion criteria:

All patients presenting the following features will be excluded from the study:

1. Known coronary anatomy with planned complex percutaneous coronary intervention with high probability of large amount of contrast use (>150 ml).
2. Moderate to severe impairment of renal function (eGFR<45 ml/min).
3. Moderate to severe impairment of liver function (Child-Pugh class B or C).
4. Severely impaired left ventricular ejection fraction (LVEF <35%).
5. Patients undergoing primary percutaneous coronary intervention (i.e., patients presenting with ST elevation myocardial infarction).
6. Severe to very severe chronic obstructive pulmonary disease (GOLD class 3 to 4).
7. Patients scheduled for cardiac surgery in the following 5 days.
8. Inability to provide informed consent.

9. STUDY PROCEDURE

The aim of the study is to evaluate if metformin continuation in diabetic patients undergoing coronary angiography could lead to an increase in lactic acid values. Clinical, laboratoristic, and echocardiographic data will be collected in order to evaluate the presence and the eventual impact on the risk of increased lactic acid values. All these data will be collected in an anonymous form at the Cardio Center of the Humanitas Research Hospital, via Manzoni 56, Rozzano (MI). We will add lactic acid to all the routinely laboratoristic parameter collected before and after coronary angiography in our center.

9.1. Patients instructions

All patients potentially enrolled will be informed regarding the study and will have to sign an informed consent before the inclusion in the study. A time schedule of study procedure is resumed in Table 1.1

9.2. Pre-enrollment and pre-procedure evaluation (baseline)

Before the inclusion, all patients will undergo to:

1. Medical history and physical examination;
2. Hemocrome, kidney and liver function, lactic acid evaluation at venous sample;
3. CK-MB, hs-troponin I, BNP evaluation at venous sample;
4. Transthoracic echocardiography;
5. 12-leads electrocardiogram.

9.3. Post-procedure evaluation (the same day after coronary angiography and before hospital discharge)

During postprocedure monitoring (after coronary angiography and before discharge) the following clinical, laboratoristic, and echocardiographic data will be collected:

1. Hemocrome, kidney and liver function, lactic acid evaluation at venous blood sample;
2. CK-MB, hs-troponin I, BNP evaluation at venous blood sample;
3. Transthoracic echocardiography;
4. 12-leads electrocardiogram.
5. Lactic acidosis, death, kidney failure, liver failure

9.4. Follow up

All patients will undergo a venous blood sample and will be contacted by phone call (if already discharged) to collect the following data:

1. Hemocrome, kidney and liver function, lactic acid evaluation at venous blood sample;
2. Lactic acidosis, death, kidney failure, liver failure

Visit schedule and data that will be collected are resumed in Table 1.1.

10. ADVERSE EVENT RISK/BENEFIT NOTIFICATION

10.1. Adverse event

According to the 2018 ESC guidelines on myocardial revascularization and literature data, there should not be an augmented risk for lactic acidosis in those patients that will satisfy our inclusion and exclusion criteria.

10.2. Cause of study withdrawal

All patients that will develop CIN will suspend metformin, as recommended by the 2018 ESC guidelines on myocardial revascularization.

11. STATISTICAL ANALYSES

11.1. Methods

Continuous variables will be reported as mean ± standard deviation and compared with Student's t test or Mann–Whitney or Wilcoxon tests on the basis of normality of data verified by Kolmogorov–Smirnov goodness-of-fit test. In case of non-normal distribution, variables will be reported as median and interquartile range (IQR). For the primary endpoints of postprocedure lactic acid values, also 95% confidence intervals will be reported. Categorical variables are reported as N (%) and will be compared with $\chi 2$ test without Yates correction for continuity or the Fisher exact test as appropriate. Subgroup analyses will be performed to assess eventual differences in the following subgroups:

- Patients taking other antiglycaemic drugs on top of metformin.
- Patients requiring percutaneous coronary angioplasty.
- Patients with mild and moderate renal function impairment (eGFR<90 and <60 ml/min).

- Patients undergoing urgent coronary angiography (<24 hours from the index event).

Furthermore, linear regression will be performed to assess the correlation between clinical, laboratoristic, and echocardiographic variables with postprocedural lactic acid values.

11.2. Level of significance

Statistical test will be used to:

- to refuse the null hypothesis of lack of association between metformin continuation and postprocedural increase of lactic acid of 20% from baseline values (primary endpoint) and our secondary endpoints (Ho = metformin continuation not associated with the endpoint)

Association between variables or events will be set at probabilistic level of 5% (p value< 0.05)

12. ETHICAL IMPLICATIONS

12.1. General rules

This study will be conducted based on Good Clinical Practices (GCP) and following all Helsinki Declaration principles

12.2. Informed consent

Every enrolled patient will sign and write the data on the approved format of informed consent after explanation of all study related procedures.

13. DATA USE AND PUBLICATION

At the end of data collection and statistical analysis, obtained data will be used for potential publication on internationl scientific journals.

14. REFERENCES

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