AN INTERVENTIONAL STRATEGY FOR NON-CULPRIT LESIONS WITH MAJOR VULNERABILITY CRITERIA IDENTIFIED BY OPTICAL COHERENCE TOMOGRAPHY IN PATIENTS WITH ACUTE CORONARY SYNDROME (THE INTER-CLIMA TRIAL)

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INTER-CLIMA study

(Treatment strategy for non-culprit lesions with vulnerability criteria in patients with acute coronary syndrome)

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NAME OF THE CENTER: San Giovanni Hospital

Patient Information Sheet

Dear Sir / Madam

You are hereby asked to participate in this research study comparing Optical Coherence Tomography (OCT) with Fractional Flow Reserve (FFR) in evaluating lesions assessed as of uncertain significance at coronary angiography.

In some cases, coronary angiography leaves doubts. In particular, intermediate grade narrowings are difficult to assess if functional intravascular assessment techniques such as FFR, IFR, RFR or morphology test such as optical coherence tomography (OCT) are not used.

OCT is an imaging technique that allows to study the size and composition of coronary plaques more accurately than standard angiography, while the evaluation of the coronary flow reserve (FFR-IFR-RFR) is a method that allows to determine more accurately if a coronary stenosis causes a significant obstacle to the passage of blood flow.

The physician who proposes you to participate in this study will use one of these two methods to decide whether to implant a drug eluting stent (a metal prosthesis covered with a small amount of drug that slowly dissolves) as a treatment for narrowing in the coronary arteries identified during coronary angiography.

Both OCT and functional evaluation (FFR, IFR, RFR) have been used for years and validated. They are also considered safe, having a very low procedural risk, and usually do not involve any symptoms. If an FFR assessment is performed, you will be given iv adenosine, a drug that can lead to a sensation of heat and a transient lowering of blood pressure.

This form explains why this study has been designed and what your role will be if you decide to participate. The module describes the possible risks associated with participation in this study, in addition to the benefits.

WHAT IS THE AIM OF THIS STUDY?

The INTER-CLIMA study aims to determine whether the precise assessment of coronary atherosclerosis using Optical Coherence Tomography (OCT) is able to provide useful information for reducing the coronary risk of patients. In particular, the INTER-CLIMA study aims to evaluate whether a strategy for the treatment of angiographically non-critical coronary lesions based on the presence of plaque vulnerability criteria can decrease the incidence of new coronary events.

Currently in patients with acute (e.g., heart attack) or chronic (e.g., stable angina) coronary syndrome, it is recommended to treat the coronary lesion responsible of the clinical scenario and to evaluate with

functional assessment (FFR/iFR/RFR) the other intermediate and not critical lesions at angiography coronary (i.e., stenosis from 40% to 70%).

Among the various methods for assessing these so-called intermediate lesions, functional assessment (FFR-IFR-RFR) is currently the reference invasive method. In fact, the treatment of only lesions capable of causing myocardial ischaemia (i.e. FFR <0.80), has been shown to optimize procedural costs but also to reduce the risk of cardiovascular events including angina and new coronary interventions. It remains to be understood whether this method can reduce more important events such as cardiac death and myocardial infarction. Such events occur more often in patients who, as in your case, are hospitalized for acute coronary syndrome.

Several studies have shown how, in the context of an acute coronary syndrome, intermediate plaques with characteristics of instability (e.g., presence of abundant lipid tissue and / or inflammatory infiltrates) can undergo a rapid evolution and cause a new acute event in about 6% of cases in the first year only. The OCT technique is able to study atherosclerosis in depth and to evaluate and quantify the lipid and inflammatory components. It may therefore be superior to functional assessment (FFR-IFR-RFR) in assessing the risk of major cardiac events in the years following your hospitalization.

WHAT DOES THIS STUDY MEAN FOR ME?

The INTER-CLIMA study aims to compare the functional approach (FFR-IFR-RFR guided) and the morphological assessment of plaque instability characteristics (OCT guided) for the choice of treatment of intermediate lesions (of uncertain significance) in patients with the acute coronary syndrome.

In practice, all intermediate lesions not directly responsible for the acute clinical event will be randomized to a functional evaluation (FFR-IFR-RFR) or to an evaluation by OCT to establish their instability and the risk of rapid progression. During the randomization process, you will be randomly assigned to one of the two groups. Randomisation is equivalent to a coin toss in which chance decides which patient group you will be assigned to. Each randomized group will include up to 710 patients and you will have an equal chance of being in one of the groups. It will be a computer program that determines the group in which you will be inserted. This process helps to avoid influences from doctors in order to make the procedures and results of the study more impartial.

The choice of treatment in both cases will be made according to pre-established criteria based on available clinical evidence and, where present, on the recommendations of current guidelines. Specifically, only functionally significant (and therefore considered important) lesions at functional evaluation (FFR-IFR-RFR) or with an OCT high-risk aspect (at least three plaque instability criteria) will be treated with angioplasty and placement of drug eluting stents). Intermediate lesions without these features will instead be treated conservatively with medical therapy. If you are in the OCT enrolment arm, a functional evaluation using RFR will be performed after the OCT assessment. However, operators will not be aware of the functional evaluation with RFR, which therefore has only a cognitive role within the research.

Many of the tests in this study are part of routine care and may be done regardless of your participation in the study. All additional tests will be specifically communicated to you by the doctors involved in the study.

As a participant of the study, you will undergo periodic medical checks, as guaranteed for all patients treated at our Center, and you will be offered the possibility of a direct telephone contact for any updates on your state of health. The study provides for a follow-up by telephone contract and / or medical examination up to 7 years from the date of enrolment.

HOW WILL THE COLLECTED DATA BE TREATED?

All data relating to the intermediate lesions identified will be recorded in a specific database together with the other clinical data of the patient and his state of health for the next 7 years. In this way it will be

possible to verify and compare the impact of the two approaches in preventing the risk of future cardiac events (e.g., heart attack). This comparison could translate into a clinical advantage and a better personalization of therapeutic and prevention strategies for patients.

We therefore ask for your consent to the processing of personal data; your name, the data collected, and the results of the analyses carried out will be kept by the managers of the Operational Unit and of the research in a confidential and private manner and will never be disclosed as single data, nor for purposes unrelated to the research area for which consent was given. In particular, pursuant to Article 10 of Law No. 196 of 2003 on the protection of people's privacy with regard to the processing of personal data, your data will be collected and stored electronically and will be used exclusively for scientific research purposes. The results of the studies that may derive from this archive may be the subject of publications in specialist medical journals, but the identity of the patients will always remain secret. At any time, you will be able to know which data are used and will be able to update and / or modify inaccurate data. All the information deriving from this study will be available upon request and will be communicated directly if there are indications that can improve the clinical treatment of the enrolled patients.

If you decide to participate in the study, the sponsor of the study (Centro per la Lotta contro L'Infarto) and other subjects collaborating with the study, such as the staff involved and the Ethics Committee (EC), will access your health information. The EC is a group of subjects who perform independent study analyses as required by the laws governing this type of study. Representatives of sponsors, EC and the competent authorities can inspect your medical records.

The sponsor may also share information with its research partners or companies it hires to offer study-related services. The information received during the study will not be used for any mailing list, nor will it be sold for commercial or marketing purposes.

A description of this clinical trial will be made available at https://www.ClinicalTrials.gov. This website, which can be consulted at any time, will not contain any information that allows you to be identified.

WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS?

This is a study that systematizes but does not substantially change the treatment of patients who in our Center are routinely subjected to invasive coronary procedures with the aid of intravascular imaging (OCT) or functional tests (FFR). The devices used in this study are CE marked and commercially available. Both OCT and functional evaluation (FFR, IFR, RFR) have been in use for years. They are also considered safe, having a very low procedural risk, and usually do not involve any symptoms. If an FFR assessment is performed, you will be given iv adenosine, a drug that can cause a sensation of heat and a transient lowering of blood pressure.

The approved devices used for the study will be used in accordance with the approved intended use and instructions for use. The study physician will inform you in detail about the risks associated with a coronary angiography and stent implantation procedure (percutaneous coronary intervention, PCI) guided by functional assessment with FFR-IFR-RFR or OCT.

WHAT ARE THE POSSIBLE BENEFITS FOR YOU OR OTHERS?

The possibility of evaluating coronary stenosis of uncertain significance with intravascular methods (FFR or OCT) represents an advantage. In fact, they are not always carried out even if the use of the FFR technique is encouraged by the guidelines. In addition, the clinical check-up repeated annually (with a visit or by telephone) represents a second advantage as it will allow doctors to monitor your conditions over time.

Finally, the results of the study could help improve the treatment of coronary heart disease through better personalization of therapeutic and prevention strategies for patients.

We also specify that you will not receive any compensation for having participated in this research study.

WHAT HAPPENS IF I DON'T WANT TO PARTICIPATE IN THIS STUDY OR WITHDRAW MY CONSENT?

In case of non-acceptance, you will be guaranteed the same assistance regardless of your participation in the study. Your study doctor will explain the other options available to you.

Even if accepted, you will have the right at any time and for any reason to leave the study without renouncing your right to assistance from the doctors involved in the study.

If you wish to terminate your participation in this research study, for any reason, please contact Dr. _____ at __-_____.

If you withdraw your consent during the study, no further information will be collected beyond that already obtained which will in any case be kept, ensuring the correct evaluation of the results of the research study project and compliance with the law. Please note that the data collected by the sponsor up to the time of your withdrawal remains part of the study results.

WHAT WOULD HAPPEN IF YOU ARE INJURED FROM THIS STUDY?

If you have any injuries, illnesses or complications that arise as a direct result of participating in this study, you will be entitled to medical treatment. In relation to these injuries, there are no agreements for any other type of compensation (for example, unpaid salary, lost time or inconvenience). However, by signing this form, you do not in any way waive your rights under the law against the sponsor, investigators or third parties, and you do not release the study physicians or other participating Centers of their legal and professional responsibilities.

The study sponsor will not cover the costs of injuries to the extent that they are caused by the doctor or hospital or reasearcher not following the study instructions, or if they are caused by a natural progression of an underlying medical condition (diagnosed or not) or pre-existing, or whether those injuries are caused by standard treatment events using currently approved therapies for your condition, unless unintentional error occurs.

WHO ORGANIZES AND FINANCES THE RESEARCH STUDY?

This research study is organized and funded in Italy by the Centro per la Lotta contro L'Infarto - CLI Foundation which will bear the additional costs of the study.

WHO CAN I CONTACT IF I HAVE QUESTIONS?

For any questions about the study or participation in it, contact doctor _____ at number ___-_____. Also, if you have any concerns, complaints or questions about your rights as a research study patient or about an injury that you believe has been caused by the study, contacts:

Name of the person at the EC: _____

EC telephone number: _____

E-mail of the EC, if known: _____

INFORMED CONSENT OF THE INTER-CLIMA STUDY

(version n.1 - approved by the Lazio 2 Ethics Committee)

Trial Prot .____

n. patient identification: _____

I, the undersigned _____

I declare:

- to voluntarily participate in the study indicated in question

- to have understood that the study involves experimental (randomized) research

- to have understood the purposes of this study and to have been informed about the procedures to which I will be subjected and about the possible foreseeable risks or inconveniences

- to have understood the reasonably expected benefits and the absence of additional expected expenses for study participants

- to have had the opportunity to be informed about every particular aspect of the study by my doctor or other trusted person.

- that I have received the name and telephone number of one or more doctors in charge of the study whom I can contact for any problems.

to be aware:

- that participation in the study is voluntary, that I can withdraw at any time and that in my interest, the doctor can decide whether to withdraw from the study without any penalty or loss of any benefits;

- that the Ethics Committee _____ of the Local Health Authority _____ has approved the experimental research protocol;

- that the monitor (s), or the auditor (s), the IRB / IEC and the regulatory authorities will be allowed direct access to my original medical documentation for a verification of the clinical study procedures and / or data , without violating confidentiality to the extent permitted by applicable laws and regulations and that, by signing an informed consent form, the participant or his or her legally recognized representative is authorizing such access;

- that the documentation identifying the participant in the subject study will be kept confidential and, to the extent permitted by applicable laws and / or regulations, will not be made publicly available.

- that the data will be stored and disclosed exclusively for scientific purposes and in anonymous form;

- that the data can be corrected or deleted at my request.

- that the participant in the study, or his legally recognized representative, will be promptly informed if information becomes available that could influence the subject's willingness to continue participating in the study;

- that the overall duration of the study period is 7 years with a total enrolment of approximately 1410 patients

Therefore, I freely consent to participate in the clinical study.

Patient's signature or Representative's signature legally recognized

_____ _____

Date: ____ / ____ / _____

I also declare that I have been informed about the contents of this study by the investigator Dr. _____ the same has answered all my questions in a comprehensive way.

I have read the above information and have had opportunity to ask questions and all my questions have been fully answered.

I freely and voluntarily accept to participate in the study. I receive a copy of this document while the original will remain in the records ".

Therefore I freely consent to participate in the clinical study.

Patient's signature or Representative's legally recognized signature

_____ _____

Date: ____ / ____ / _____

TO BE FILLED IN BY THE DOCTOR WHO CONDUCTED THE INTERVIEW

I, the undersigned, confirm that I have explained to the patient the characteristics of the study, the nature, the purpose and the potential benefits / risks related to the study and the right he has to interrupt the study at his request at any time, and in good conscience I believe that he has understood them.

I confirm that the patient has freely accepted to participate in the study by signing the appropriate consent form; that this form will be filed at our research Center as per current legislation and I declare that I have delivered a copy to the patient.

Surname and first name of the doctor who conducted the consent interview:

_____

(In capital letters)

Doctor's signature _____ Date _____ / _____ / _____