INTER-CLIMA TRIAL

(An Interventional Strategy for Non-culprit Lesions With Major Vulnerability Criteria Identified by Optical Coherence Tomography in Patients With Acute Coronary Syndrome)

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PATIENT INFORMATION SHEET

Dear Sir/Madam,

you are being asked to participate in this research study that compares Optical Coherence Tomography (OCT) with the assessment of coronary flow reserve (FFR – Fractional Flow Reserve) in the evaluation of coronary lesions of uncertain significance on coronary angiography.In some cases, coronary angiography leaves doubts. In particular, intermediate-grade stenoses are difficult to assess unless intravascular evaluation techniques are used, either functional (FFR, iFR, RFR) or morphological such as Optical Coherence Tomography (OCT). OCT is an imaging technique that allows for a more accurate assessment than standard angiography of the size and composition of coronary plaques, while coronary flow reserve assessment (FFR, iFR, RFR) is a technique that allows to more accurately determine whether a stenosis causes a significant obstacle to blood flow. The physician proposing your participation in this study will use one of these two techniques to decide whether to implant a drug-eluting stent (a metallic prosthesis coated with a small amount of drug that slowly dissolves) to treat narrowings in the coronary arteries identified during coronary angiography. Both OCT and functional assessment (FFR, iFR, RFR) have been used and validated for years. They are also considered safe, with a very low procedural risk, and they generally do not cause any symptoms. In the case of FFR assessment, intravenous adenosine will be administered—a drug that may cause a sensation of warmth and a temporary drop in blood pressure. This document explains the reason why this study was designed and what your role will be should you decide to participate. In addition to potential benefits, it also describes the possible risks associated with participation in this study.

WHAT IS THE PURPOSE OF THIS STUDY?

The INTER-CLIMA study aims to determine whether an accurate assessment of coronary atherosclerosis using Optical Coherence Tomography (OCT) can provide useful elements for reducing the coronary risk of patients. In particular, the INTER-CLIMA study aims to evaluate whether a treatment strategy of angiographically non-critical coronary lesions based on the presence of plaque vulnerability criteria is able to reduce the incidence of new coronary events. Currently, in patients with acute coronary syndrome (e.g. myocardial infarction) and chronic coronary syndrome (e.g. stable angina), treatment of the lesions responsible for the clinical condition and a functional assessment of any intermediate and non-critical lesions on angiography (i.e. 40% to 70% stenoses) is recommended. Among the various methods used to assess these so-called intermediate lesions, functional assessment (FFR, iFR, RFR) is currently the invasive reference technique. In fact, treating only those lesions that can cause myocardial ischemia (i.e. FFR < 0.80) has been shown to optimize procedural costs as well as reduce the risk of cardiovascular events, including angina and new angioplasty procedures. It still remains to be determined whether this method can also reduce more significant events such as cardiac death and myocardial infarction. These events occur more frequently in patients who, like yourself, have been hospitalized for an acute coronary syndrome. Several studies have shown that, in the setting of acute coronary syndrome, intermediate plaques with features of instability (e.g. presence of abundant lipid tissue and/or inflammatory infiltrates) can undergo rapid evolution and cause a new acute event in about 6% of cases within just the first year. The OCT technique is capable of thoroughly assessing atherosclerosis and evaluating and quantifying lipid and inflammatory components. It could therefore prove superior to functional assessment (FFR, iFR, RFR) in evaluating the risk of major cardiac events in the years following your hospitalization.

WHAT DOES THIS STUDY INVOLVE FOR ME?

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

In practice, all intermediate lesions not directly responsible for the acute clinical event will be randomized to a functional assessment (FFR, iFR, RFR) or to an OCT evaluation. During the

randomization process, you will be assigned by chance to one of the two groups. Randomization is equivalent to flipping a coin, where chance determines to which group you will be assigned. Each randomized group will include up to 710 patients, and you will have the same probability of being in either group. A computer program will assign you to one group. This process helps avoid any influence from the physicians in order to make the procedures and the results of the study more objective.

The choice of treatment in both cases will be carried out according to pre-established criteria based on available clinical evidence and, where applicable, on current guideline recommendations. Specifically, only functionally significant lesions (and therefore judged important) at functional evaluation (FFR, iFR, RFR) or those with high-risk features at OCT will be treated with angioplasty and placement of drug-eluting stents. Intermediate lesions without these characteristics will instead be treated conservatively with medical therapy. Many of the tests in this study are part of routine care and could be performed regardless of your participation in the study. Any additional tests will be specifically communicated to you by the physicians involved in the study. As a study participant, you will be scheduled for regular medical check-ups, as is guaranteed to all patients treated at our center, and you will be offered the possibility of direct phone contact for any updates concerning your health status. The study includes follow-up by phone and/or medical visits for up to 7 years from the enrollment date.

HOW WILL THE DATA COLLECTED BE HANDLED?

All data relating to the identified intermediate lesions will be recorded in a dedicated database along with the other clinical data of the patient and their health status over the next 7 years. This will allow us to verify and compare the impact of the two approaches in preventing the risk of future cardiac events (e.g. myocardial infarction). This comparison could lead to a clinical advantage and better personalization of therapeutic and preventive 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 conducted will be stored by the heads of the Clinical Unit and the research team in a confidential and private manner and will never be disclosed as individual data, nor used for purposes unrelated to the research field for which consent was given. Specifically, pursuant to Art. 10 of Law No. 196/2003 on the protection of individuals regarding 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 studies that may derive from this database may be published in medical journals, but the identity of the patients will always remain confidential. At any time, you may know

which data are being used and may update and/or correct inaccurate data. All information resulting from this study will be available upon request and will be directly communicated if findings emerge that may improve the clinical management of enrolled patients.

If you decide to participate in the study, the study sponsor (the "Centro per la Lotta Contro l'Infarto") and other entities collaborating with the study, such as the involved personnel and the Ethics Committee (EC), will access your medical information. The EC is a group of individuals who conduct independent review of the study as required by laws governing this type of research. Representatives of the sponsor, the EC, and the competent authorities may inspect your medical records. The sponsor may also share information with its research partners or companies contracted to provide services related to the study. Information obtained during the study will not be used for mailing lists, nor sold for commercial or marketing purposes. The Data Protection Officer (DPO) of the center is Dr. Francesco Prati, available at the phone number 06-77055710. A description of this clinical trial will be made available at the following address: https://www.ClinicalTrials.gov. This website, accessible 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 modify the treatment of patients who are routinely subjected, in our center, to invasive coronary procedures with the support of intravascular imaging (OCT) or functional tests (FFR). The devices used in this study are CE-marked and commercially available. Both OCT and functional assessment (FFR, iFR, RFR) have in fact been in use for years. They are also considered safe, having a very low procedural risk, and they generally do not cause any symptoms. In the event that FFR assessment is performed, intravenous adenosine will be administered—a drug that may cause a sensation of warmth and a temporary drop in blood pressure.b The approved devices used in the study will be used in accordance with the approved intended use and the instructions for use. The study physician will inform you in detail about the risks associated with a coronary angiography procedure and with stent implantation (Percutaneous Coronary Intervention, PCI) guided by functional assessment with FFR, iFR, RFR or by OCT.

WHAT ARE THE POSSIBLE BENEFITS FOR YOU OR OTHERS?

The possibility of evaluating coronary stenoses of uncertain significance with intravascular techniques

(FFR or OCT) represents an advantage. In fact, they are not always performed, although the use of the FFR technique is encouraged by the guidelines. Furthermore, repeated clinical monitoring on an annual basis (by visit or phone) represents a second benefit as it will allow physicians to monitor your condition over time. Finally, the results of the study could help improve the treatment of coronary artery disease through better personalization of therapeutic and preventive strategies for patients. We also specify that you will not receive any compensation for participating in this research study.

WHAT HAPPENS IF I DO NOT WISH TO PARTICIPATE IN THIS STUDY OR WITHDRAW MY CONSENT?

If you do not accept, you will be guaranteed the same assistance regardless of your participation in the study. The study physician will explain to you the other options available to you. Even if you accept, you will have the right at any time and for any reason to withdraw from the study without forfeiting your right to care from the physicians involved in the study. If you wish to discontinue participation in this research study for any reason, please contact Dr. _____ at the number _____.

If you withdraw your consent during the study, no further information will be collected beyond what has already been obtained, which will nevertheless be retained to ensure the correct evaluation of the research study results and compliance with legal provisions. Please note that the data collected by the sponsor up to the time of your withdrawal remain part of the study results.

WHAT WOULD HAPPEN IF I SUSTAIN INJURIES AS A RESULT OF THIS STUDY?

In the event of injuries, illness, or complications arising directly from participation in this study, you will be entitled to medical treatment. No other compensation arrangements have been made (for example, lost wages, time lost, or inconvenience). However, by signing this form, you do not waive any of your legal rights against the sponsor, the investigators, or third parties, nor do you release the study physicians or other participating centers from their legal and professional responsibilities.

The study sponsor will not cover the costs of injuries to the extent that they are caused by your failure to comply with study instructions, by the hospital or study physician’s non-compliance, by the natural progression of a pre-existing pathological condition (whether diagnosed or not), or by events inherent to the standard treatment using currently approved therapies for your condition, except in cases of

inadvertent error.

WHO ORGANIZES AND FUNDS THE RESEARCH STUDY?

This research study is organized and funded in Italy by the Fondazione Centro per la Lotta Contro l'Infarto.

WHO CAN I CONTACT IF I HAVE QUESTIONS?

For any questions about the study or your participation, contact Dr. _____ at _____.

Also, for any doubts, complaints, or questions about your rights as a patient in a research study or regarding any injury you believe was caused by the study, please contact:

Ethics Committee Contact Person: _____

Phone Number: _____

Email (if known): _____

INTER-CLIMA STUDY INFORMED CONSENT

Protocol No.: _____

Patient Identification No.: _____

I, the undersigned, _____,

declare that:

- I voluntarily agree to participate in the above-mentioned study.
- I understand that the study involves experimental (randomized) research.
- I have understood the purposes of this study and have been informed about the procedures to which I will be subjected and the possible foreseeable risks or discomforts.
- I have understood the reasonably expected benefits and the absence of any additional costs for study participants.
- I have had the opportunity to inquire about every particular aspect of the study with my treating physician or another trusted person.
- I have received the name and telephone number of one or more study physicians whom I can contact for any problems.

I am aware that:

- Participation in the study is voluntary, that I may withdraw at any time, and that, in my interest, the physician may decide to withdraw me from the study without penalty or loss of potential benefits.
- The Ethics Committee of the Local Health Authority has approved the experimental research protocol.
- Monitors, auditors, the IRB/IEC, and regulatory authorities will be allowed direct access to my original medical records for verification of clinical study procedures and/or data, without violating confidentiality to the extent permitted by applicable laws and regulations, and that by signing this informed consent form, I am authorizing such access.

- Documents identifying me as a study participant will be kept confidential and, to the extent permitted by applicable laws and regulations, will not be publicly disclosed.
- Data will be stored and disclosed exclusively for scientific purposes and in anonymized form.
- Data may be corrected or deleted at my request.
- I or my legally authorized representative will be promptly informed if information becomes available that may affect my willingness to continue participating in the study.
- The total duration of the study period is 7 years with a total enrollment of approximately 1,410 patients.

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

Patient's Signature or **Legal Representative's Signature**: _____
Date: ___ / ___ / _____

I also declare that I have been informed about the contents of this study by the investigator Dr. _____, who has answered all my questions thoroughly. I have read the above information and have had the opportunity to ask questions, all of which have been answered to my satisfaction. I freely and voluntarily agree to participate in the study. I receive a copy of this document, and the original will remain on file.

Patient's Signature or **Legal Representative's Signature**: _____
Date: ___ / ___ / _____

TO BE COMPLETED BY THE PHYSICIAN WHO CONDUCTED THE CONSENT DISCUSSION

I, the undersigned, confirm that I have explained to the patient the characteristics of the product, the nature, purpose, and potential benefits/risks of the study, and the right to withdraw from the study at any time upon request, and I sincerely believe that the patient has understood them.
I confirm that the patient has freely agreed to participate in the study by signing the informed consent form; that this form will be archived at our research center in accordance with applicable regulations; and that I have provided a copy to the patient.

Physician's Name (printed): _____
Signature: _____
Date: ___ / ___ / _____