SYNOPSIS OF THE STUDY CHARACTERISTICS

STUDY TITLE: *"Functional versus Culprit-only Revascularization in Elderly Patients with Myocardial Infarction and Multivessel Disease" FIRE Trial*

PRESPECIFIED SUBSTUDY TITLE: "Gauging Of Lipid content and DEtermination of microcirculatory impairment in functionally negative Non-culprit arteries in elderly patients with NSTEMI enrolled in the FIRE trial" (the GOLDEN-FIRE)

Number of registration: *clinicaltrials.gov NCT03772743*

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Sponsor: *Consorzio Futuro in Ricerca*

Study duration: *24 months of enrollment, 12 months for the follow-up of the last patient enrolled*

BACKGROUND

Recently, the safety of deferral revascularization by means of coronary physiology in non-culprit lesions in acute coronary syndrome (ACS) setting has been questioned[1].

A total of 8,579 patients were included in the analysis, 6,461 with chronic coronary syndrome (CCS) and 2,118 with ACS and non-culprit stenoses. Using fractional flow reserve (FFR), revascularization was deferred in 5,129 patients (59.8%) and performed in 3,450 patients (40.2%). In the deferred ACS group, a higher MACE rate was observed compared with the deferred SAP group (4.46% vs. 2.83%; adjusted hazard ratio [HR]: 1.72; 95% confidence interval [CI]: 1.17 to 2.53; $p < 0.01$) [1].

This is probably due to the higher intrinsic risk of adverse events in the ACS setting compared to the stable one.

However, it is theoretically possible that functional assessment may overlook some stenoses causing clinical events in the follow-up through two different mechanisms:

i) A false negative evaluation due to a temporary and reversible microcirculatory impairment due to ACS;
ii) The fact that mild and non-flow limiting stenoses are more likely to evolve in unstable plaques

To this hand, invasive evaluation of microcirculatory function is easy and reliable and intravascular imaging has been implied since a long time in trying to detect vulnerable plaques. In particular, at near infrared spectroscopy, a cut-off of maximum lipid core burden index (LCBI) within 4 mm (LCBI max 4 mm)>400 emerged as the single surrogate marker able to identify the lipid-rich plaques (LRP)[2].

Thus, in order to assess whether the higher risk of adverse events in d deferred lesions in the acute setting is due to the different clinical setting or not, it would be of interest to evaluate the rate of non-culprit lesions with negative functional assessment and a max LCBI 4 mm value >400 and/or with microcirculatory impairment (IMR>25) and to investigate whether their presence is related to a worse outcome in elderly NSTEMI patients with at least one non-culprit lesion deferred with coronary physiology.

STUDY RATIONALE

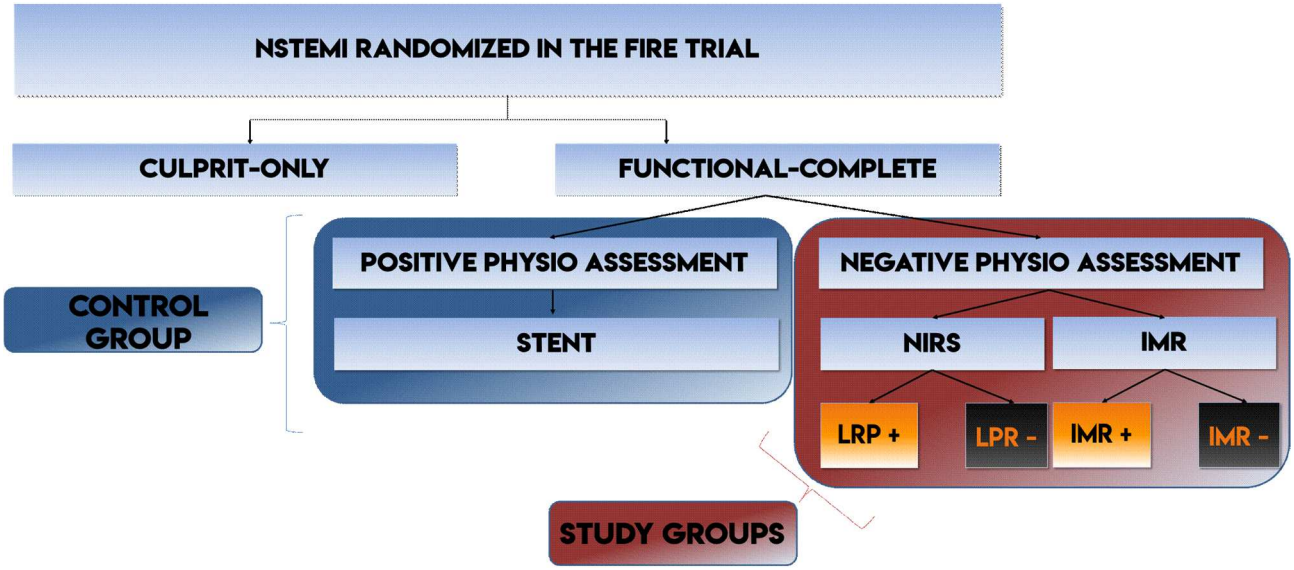
The benefit of complete revascularization in older MI patients is debated and the utility of functional assessment in deferring treatment of non-culprit lesion in the same setting is questioned. NSTEMI setting is particularly neglected in terms of studies aimed at the investigation of the strategy to pursue in non-culprit lesions.

The detection of LRP by NIRS and of microcirculatory dysfunction may identify non-culprit lesions functionally non-significant, but associated with adverse events in the follow-up in elderly NSTEMI patients.

Thus, the NEXT-FIRE study is aimed to evaluate:

1. The percentage of non-culprit with functional assessment negative lesions that are identified as "vulnerable plaques" (LCBI max 4 mm≥400).
2. The percentage of non-culprit with functional assessment negative lesions with relevant microcirculatory dysfunction.
3. The rate of vessel oriented composite endpoint (VOCE) in non-culprit lesions with negative functional assessment according to LCBI max 4 mm value (≥400 vs <400) and microcirculatory dysfunction presence (>25 versus ≤25) in non-culprit lesions treated because of a positive functional assessment.

STUDY FLOW CHART



OBJECTIVES

To evaluate:

- The rate of non-culprit lesions with negative functional assessment and LRP (LCBI max 4 mm>400) and/or with microcirculatory dysfunction (IMR>25);
- Whether the outcome of non-culprit lesions (vessel oriented composite endpoint [VOCE]) deferred with functional assessment is different among patients with LRP (LCBI max 4 mm>400) or microcirculatory dysfunction (IMR>25) and patient without them in patients with NSTEMI and MVD randomized to functional complete revascularization in the FIRE trial.

INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria:

1. Patients ≥ 75 years AND
2. **NSTEMI with indication to invasive management AND**
3. Multi-vessel disease defined as at least 1 non-culprit coronary artery lesion at least 2.5 mm in diameter deemed at visual estimation with a diameter stenosis % ranging from 50 to 99% amenable to successful treatment with PCI AND
4. Successful treatment of culprit lesion AND
5. Signed informed consent
6. **Randomization to complete strategy with at least one functional negative assessment**

Exclusion Criteria:

1. Planned surgical revascularization
2. Left main as location of the non-culprit lesion
3. Non-cardiovascular co-morbidity reducing life expectancy to < 1 year
4. Any factor precluding 1-year follow-up
5. Prior Coronary Artery Bypass Graft (CABG) Surgery
6. Impossibility to identify a clear culprit lesion

STUDY PROCEDURES

Functional assessment

In the FIRE trial, we include different systems for the evaluation of coronary physiology. In particular, we considered as equivalent FFR and adenosine free-indices such as instantaneous wave-free ratio (iFR), contrast FFR (cFFR), and angiography-derived-FFR. Functional assessment will be then performed according to local practice with one of the above mentioned technologies.

Index of Microcirculatory Resistance (IMR)

Index of Microcirculatory Resistance (IMR) is a reliable and validated quantitative method to assess cardiac microcirculatory function[3]. IMR was obtained on one single occasion according to the method previously described[3]. IMR measurements are expressed as unit (U). Briefly, the transit time of room-temperature saline injected in a coronary artery was determined by thermodilution. Three injections of 3 ml were made, and the resting mean transit time (Tmn) was measured. After adenosine-induced maximal hyperemia, 3 more injection of 3 ml of room temperature saline were performed, and the hyperemic Tmn (Tmn_{hyp}) was measured. Mean aortic pressure by guiding catheter (Pa) and mean distal coronary pressure by a pressure wire (Pd) were evaluated both in the resting, and maximal hyperemic states ($P_{a\ hyp}$ and $P_{d\ hyp}$). IMR calculation was performed with Coroventis system (Coroventis AB, Uppsala, Sweden). A well-established cut-off for normal IMR values in patients with coronary artery disease is not available. According to values reported in previous studies, we defined a normal microcirculatory resistance if IMR value was ≤25 U.

Near infrared spectroscopy (NIRS)

Spectroscopy can be defined as the measurement of the wavelength-dependent interaction of electromagnetic radiation with matter. In particular, NIRS (near-infrared spectroscopy) is widely used to identify the chemical composition of unknown substances. In order to obtain anatomical information on the vessel and optimal plaque characterization, a hybrid technology (TVC Imaging SystemTM, InfraRedx Inc.)

combining NIRS and IVUS was further developed, which allows simultaneous, co-registered acquisition of structural and compositional data of coronary artery plaques with particular regard to lipid presence with plaque. Thus, the NIRS spectra data are mapped and paired with corresponding cross-sectional IVUS frames, presented as a ring around the IVUS image[4].

A 3.2 Fr IVUS-NIRS catheter (LipiScan™ IVUS Coronar maging System; Infraredx, Burlington, MA, USA) should be first employed to interrogate the target artery, at a speed of 0.5 mm/sec. During catheter pullback, the measurement of the probability of lipid core is displayed as an NIRS 'chemogram', a digital colour-coded map of the location and intensity of lipid core, with the X-axis indicating the pullback position in millimetres (every 0.1 mm) and the Y-axis indicating the circumferential position in degrees (every 18) as if the coronary vessel has been split open along its longitudinal axis. Spectroscopic information at each pixel is transformed into a probability of lipid core that is then mapped to a 128 (7-bit) red-to-yellow colour scale, with the low probability of lipid shown as red and the high probability of lipid shown as yellow. If a pixel does not contain enough data (e.g. as caused by guidewire shadowing), it appears black—i.e. a 'non-viable' pixel. The 'block chemogram' is a summary metric that is computed to display the probability that a lipid core plaque (LCP) is present for all measurements using the top 10th percentile pixel information (i.e. the 90th percentile value) of the corresponding 2 mm NIRS 'chemogram' segment. If the probability of the top 10th percentile is ≥0.98, the entire block is assigned yellow; if the probability of the top 10th percentile is 0.84–0.98, the entire block is assigned tan; if the probability of the top 10th percentile is 0.57–0.84, the entire block is assigned orange; if the probability of the top 10 percentile is 0.57, the entire block is assigned red. The 'block chemogram' provides a summary of the data to enhance interpretation of the chemogram and does not indicate individual pixel data or the location of a measurement in the circumferential dimension.

The presence of lipid core within the region of interest required at least one yellow block (95% specificity that lipid core was present). Yellow pixels (pixels above the preset threshold for the detection of LCP) within the analysed segment are divided by all viable pixels in the 'chemo-gram' to generate the lipid core burden index (LCBI) per 1000 (‰). Total LCBI, the 2 mm length with the maximum LCBI, and mean and maximum angles of lipid core are computed using the entire spectroscopic information within the region of interest in the 'chemogram' and exported by the NIRS software automatically.

SAMPLE SIZE CALCULATION

No formal sample size calculation can be applied since this substudy is observational[5].

We plan to include around 100 patients in the present substudy.

References

1. Cerrato E, Mejia-Renteria H, Dehbi HM, Ahn JM, Cook C, Dupouy P, et al. Revascularization Deferral of Nonculprit Stenoses on the Basis of Fractional Flow Reserve: 1-Year Outcomes of 8,579 Patients. JACC Cardiovasc Interv 2020.
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5. Wijns W, Shite J, Jones MR, Lee SW, Price MJ, Fabbiocchi F, et al. Optical coherence tomography imaging during percutaneous coronary intervention impacts physician decision-making: ILUMIEN I study. Eur Heart J 2015;36(47):3346-55.