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: "Characterization of plaque vulnerability by OCT in non-culprit lesions of older NSTEMI patients enrolled in the FIRE trial: the CAP-FIRE"

Number of registration: *clinicaltrials.gov NCT03772743*
Principal Investigator FIRE Trial*: Simone Biscaglia, MD*
Sponsor: *Consorzio Futuro in Ricerca*
Study duration: *18 months of enrollment, 12 months for the follow-up of the last patient enrolled*

BACKGROUND

The validity of deferring revascularization by means of fractional flow reserve (FFR) in non-culprit lesions (NCLs) in acute coronary syndrome setting (ACS) has been recently questioned. Cerrato et al.[1] performed a patient level analysis of 8579 patients with multivessel disease (MVD) enrolled in several studies where fractional flow reserve (FFR) was utilized to indicate or defer revascularization. They included 6461 patients with chronic coronary syndrome (CCS) and 2118 with ACS. According to the results of FFR, revascularization was deferred in 5129 patients. When stratifying patients for their clinical presentation, patients with ACS deferred by FFR showed a higher rate of MACE if compared to those deferred in CCS setting, whereas there was no difference in patients with positive FFR. Authors suggested that deferral of revascularization with FFR in ACS setting could be less safe than in CCS setting. An explanation of their result could be that FFR may overlook stenoses potentially at high developmental risk due to the temporary and reversible microvascular dysfunction during ACS with consequent hampering of hyperemia achievement. On the other end, non-obstructive stenoses could also evolve towards instability.

Pinilla-Echeverri et al. observed that in their substudy of the COMPLETE trial [2] that at least 50% of patients with ST segment elevation myocardial infarction (STEMI) and MVD had obstructive NCLs with high profile of plaque instability. However, in the COMPLETE trial, indication to revascularization was guided by angiography in lesions with diameter stenosis >70% and, therefore, no coronary physiology assessment was performed, and we do not know whether vulnerable plaques were functionally positive or negative. Thus, it would be interesting to assess whether physiology is able to discriminate plaques with OCT features of instability/vulnerability.

In fact, physiological lesion assessment by FFR might be a surrogate of vulnerable and complex lesion morphology of coronary plaques), although results are not conclusive and seem to be questioned by the above mentioned analysis [3-4].

Recent studies showed that not only FFR, but also the index of microcirculatory resistance (IMR) and coronary flow reserve (CFR) are independent predictors of the presence of OCT-defined thin cap fibroatheroma (TCFA) [5-7].

In addition, the same FFR value at the vessel level may portend completely different underlying mechanisms such as single focal lesion, serial lesions or diffuse disease. If FFR-related prediction of adverse events is related to its ability to highlight abnormal flow dynamics at the level of an unstable plaque, the physiological map of the vessel should be equally, if not more, relevant than the overall vessel value. Interestingly, several quantitative measures of the presence of focal versus diffuse disease have been recently developed by analysing FFR pullback curves [8-9]. The pullback pressure gradient (PPG) index is a continuous metric based on the magnitude of pressure drop over 20 mm and on the extent of functional disease was

computed to determine the pattern of CAD. Low PPG index indicates diffuse CAD. The instantaneous FFR gradient per unit time (dFFR(t)/dt) is another tool able to discriminate focal versus diffuse disease and to predict post-PCI physiological results. Therefore, it would be interesting to evaluate whether these measures correlate with the presence of TCFA.

In addition, among the different clinical ACS presentations, the most neglected one is by far non-STEMI. Therefore, it would be particularly interesting to focus on NCLs in NSTEMI setting.

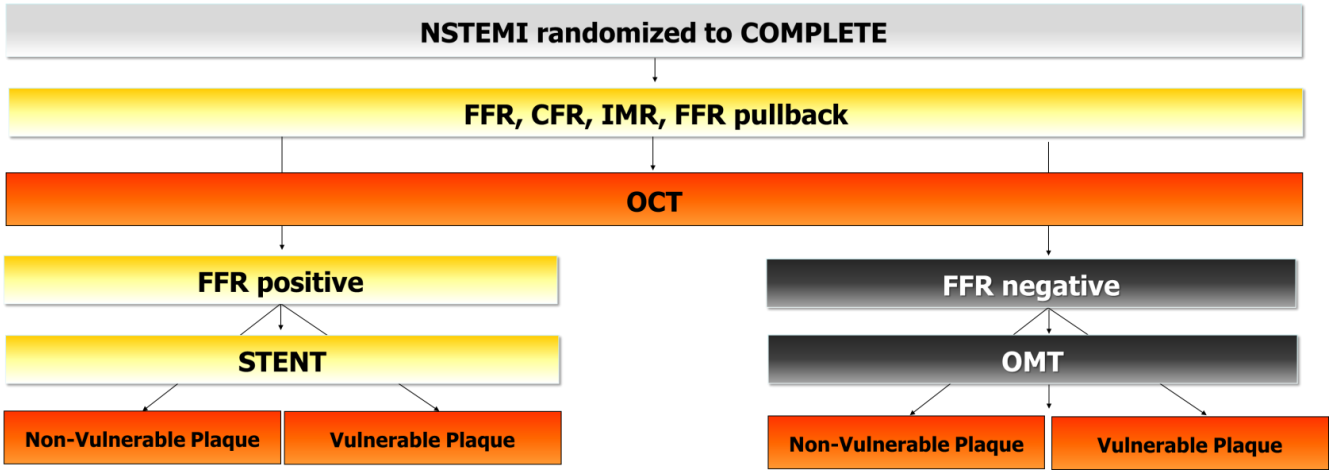
STUDY RATIONALE

FFR ability to stratify NCLs in ACS setting has been questioned. OCT is able to detect features associated with plaque vulnerability. Abnormal FFR, IMR and CFR values have been previously associated with the presence of unstable, evolving plaque. FFR pullback is able to define the underlying mechanism of abnormal FFR value in terms of presence of focal or diffuse disease with the former being associated with unstable evolving plaque.

Starting from this background, the present substudy of the FIRE trial has the following aims:

i) Evaluate whether FFR positive lesions are more frequently associated with plaque vulnerability" characteristics according to OCT if compared to FFR negative lesions;
ii) Evaluate whether CFR or IMR are more frequently associated with plaque vulnerability" characteristics according to OCT if compared to FFR;
iii) Evaluate whether the combination of FFR value and focal disease at pullback increases the ability to predict the presence of vulnerable plaque if compared to FFR alone.

STUDY FLOWCHART



OBJECTIVES

To evaluate:

- The rate of non-culprit lesions which underlying vulnerable plaques according to the characteristics of the lesion analyzed by OCT (TCFA < 65 µm, lipid arc > 90° and low MLA).
- Whether the incidence of plaque vulnerability is actually higher in functionally positive NCLs.
- Whether the presence of abnormal CFR and/or IMR values is able to improve the prediction of plaque vulnerability by FFR.
- Whether the presence of focal disease at FFR pullback is able to improve the prediction of plaque vulnerability by FFR.

INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria:

1. Patients ≥ 75 years AND
2. NSTEMI with indication to invasive management AND
3. MVD 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
7. Suitable artery for OCT imaging (vessel with >2 mm in diameter with at least 50 mm of unstented native artery available for image evaluation)

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
7. Artery unsuitable for imaging (severe calcification, marked tortuosity or chronic total occlusion)
8. Estimated glomerular filtration rate <35 mL/min per 1.73 m^2

STUDY PROCEDURES

Functional assessment

In FIRE trial we include different systems for 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. For the present substudy, CFR, IMR, FFR and FFR pullback will be evaluated via with Pressure wire X and the Coroventis console (Abbott, Santa Clara, USA).

FFR *[6]*

FFR is a validated functional index for the evaluation of intermediate lesions. Following administration of nitroglycerine, a guidewire for invasive pressure monitoring is advanced distal to the stenosis and hyperemia is induced by intravenous injection of adenosine. The FFR value is calculated by dividing the distal pressure and the mean aortic pressure (measured at the tip of the guiding catheter) during a condition of stable hyperemia.

IMR *[6]*

IMR is measured starting from hyperemic thermodilution curves and hyperemic mean transit time. Thermodilution is obtained by means of a 3 ml saline bolus injection repeated 3 times. IMR was calculated as the product of mean distal coronary pressure during stable hyperemia and hyperemic mean transit time, corrected using Yong's formula.

CFR *[6]*

Coronary flow reserve (CFR) is measured simultaneously with FFR and IMR using the thermodilution method; it is expressed as the ratio of basal mean transit time divided by hyperemic mean transit time.

FFR pullback: PPG and delta FFR/delta t *[8-9]*

The maximum PPG is defined as the maximum pressure gradient > 20 mm obtained during the manual pull-back performed at constant speed (5-6 mm/s), in order to derive the functionally significant disease length

and its type (focal or diffuse). The PPG is a continuous index, where values close to 1 represent focal stenosis and values close to 0 represent diffuse disease.

The delta FFR represents the difference between the FFR value obtained at the ostium of the vessel and the value obtained in the most distal portion of the vessel. dFFR (t)/dt reflects the instantaneous change in FFR per unit along the vessel. Performing a pull-back at constant speed, dFFR(t)/dt is proportional to dFFR(s)/ ds, which is a measure of the local change of the FRR with small variations in the point at which it is measured. In this way it is possible to obtain information on the type of coronary heart disease. Three categories of FFR gradients were considered: major, minor and signal noise. Major FFR gradients is defined by the peak value of dFFR (t)/dt corresponding to an angiographically significant stenosis (> 50%) with pressure gradients across the lesion> 15 mmHg. The signal noise is defined by the peak value of dFFR (t)/dt not corresponding to a significant stenosis and with pressure gradient across the lesion <5 mmHg. All FFR gradients that do not fall into these two categories are considered as minor.

***OCT** [10]*
Optical coherence tomography (OCT) is an intravascular imaging system that allows the acquisition of images at high resolution (about 10 micrograms) working in the near infrared range, in order to analyse the cross-sectional microstructure of the vascular wall.

The underlying principle of OCT is analogous to the IVUS's one; structural information can be derived as a function of depth within the vessel wall by measuring the delay time of echoes reflected or backscattered from subsurface.

During the angiographic study, a guidewire and the OCT catheter are placed in the vessel to be studied in distal position. Intracoronary iodinated contrast medium is injected and an automatic pullback is performed based on the characteristics of the available system.

Lesions are defined by the presence of at least one pathological quadrant in the cross-sectional frames and the composition of any plaques is analyzed in each quadrant at 1 mm intervals. Plaques are divided into lipid, fibrous or calcified using standard definitions [11]. The minimum lumen area (MLA) is calculated automatically by the software. Fibrous cap thickness (FCT) is measured in its thinnest portion in three different cross-sectional frames. Lipid arc is measured as the average of measurements taken at 1mm intervals throughout the lesion. TCFA was defined as a lesion with a mean FCT of less than 65 µm underlying a lipid plaque (with lipid arc> 90 °).

The following parameters are taken into account for the analysis of plaque instability: lesion length, number of pathological quadrants, MLA, FCT and lipid arcs.

SAMPLE SIZE CALCULATION

Being and observation study no formal sample size is needed [12]. For pilot studies the enrolment of at least 30 patients is suggested [13]. We therefore plan to include around 50 patients in the present substudy.

References

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