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: "Microcatheter- vs. Wire-based Physiology assessment before, during and after PCI of challenging non-culprit lesions of MI patients" (FullPhysio-FIRE)

Number of registration: *clinicaltrials.gov NCT03772743*
Principal Investigator*: Simone Biscaglia, MD*
Sponsor: *Consorzio Futuro in Ricerca*
Study duration: *6 months of enrollment, 12 months for the follow-up of the last patient enrolled.*

BACKGROUND

Physiology-based Percutaneous Coronary Intervention: moving toward a Full-Physio approach.

Coronary physiology was born and has been developed to discriminate intermediate lesions of patients with chronic coronary syndrome (CCS) requiring revascularization. In the last years, physiology-based percutaneous coronary intervention (PCI) expanded its applications. Pre-PCI assessment is still the major indication, but not only in CCS patients, but also in non-culprit lesions of patients with myocardial infarction (MI). In addition, physiology, through the pullback of the vessel, permits to better discriminate the pattern of coronary artery disease (focal vs. diffuse). Finally, recent evidence strongly supported its application in the post-PCI setting, to discriminate vessel with suboptimal result and requiring further intervention [1]. More than 20 years of research strongly indicated that a Full-Physio PCI should be considered the best solution for the large majority of the PCI. Coronary physiology should guide the indication to PCI for all coronary lesions, excluding culprit lesion of MI patients. Coronary physiology, illustrating the pattern of disease, should guide the extension of the PCI treatment. Finally, coronary physiology should assess if the PCI procedure has been adequate and if a good functional outcome has been achieved.

Barriers to Full-Physio PCI diffusion.

Despite many studies and randomized clinical trials, physiology-guided PCI represents a minority of the whole number of procedures. Visual estimation is still the main trigger of PCI procedures as well as the way to evaluate PCI result. The Evolving Routine in Standards of FFR (ERIS) study investigated the barriers against physiology-guided PCI diffusion [2]. The first important message is that physiology for the post-PCI assessment is poorly used. This is mainly due that its use for post-PCI assessment is related to pre-PCI assessment. It is highly unlikely to use physiology as a "pure" post-PCI tool. The second important message is that many operators consider wire-based physiology assessment feasible only in a portion of cases. In the 11% of cases

where physiology was suggested but not done, the cause was that the operator believed not feasible a wire-based assessment. In addition, it was common that operators prefered alternative tools (i.e. intracoronary imaging) because the lesion was ostial or challenging. Similarly, it not surprising that operators frequently do not perform post-PCI assessment because they prefer to avoid recrossing the stent with the wire for physiology.

TruePhysio microcatheter: an easy-to-use tool for FullPhysio-PCI

TruePhysio is a rapid exchange microcatheter for FFR assessment. TruePhysio has a ultra-thin profile and it has been designed to rapidly go in and out on work-horse wire. As compared to wire-based FFR systems, the potential main advantages of TruePhysio are:

- the position of the work-horse wire can be mantained for all the procedure
- tortuous vessels and/or challenging lesions can be crossed with the work-horse wire and investigated without the need of additional wiring
- for post-PCI assessment, recrossing of the stent is not necessary
- in case of pulback for the investigation of the pattern of disease, the work-horse wire can be mantained in position
- drift is less common
- ostial lesion can be easily investigated
- disconnection and re-connection during PCI are no more necessary.

As reported above, the indications and aims of a physiology-guided PCI are changed in the last years. Wire-based technology shows inherent limitations that cannot be overcame. A microcatheter-based technology could be the best solution to finally move toward a full-physio PCI approach.

TruePhysio microcatheter: limitations

Current evidence confirms that TruePhysio microcatheter is a reliable tool for FFR assessment. As compared to wire-based technology, TruePhysio is easier, quicker and with less drift. However, this data comes again from a study population of CCS patients with coronary lesions a low complexity. At the moment, while it is intuitive that TruePhysio can be a game changer in vessels with tortuosity, in long challenging diseases, in ostial lesions, and in patients with several comorbidities, there is no evidence to prove it. In the same way, no evidence supports the reliability of TruePhysio in the post-PCI assessment. The current gap in knowledge for TruePhysio is to demonstrate that the technical superiority, as compared to wire-based systems, permits to apply a full physiology guided PCI in all anatomical and clinical subsets.

FIRE trial: the trial of FIRE for TruePhysio microcatheter

In the "Functional versus Culprit-only Revascularization in Elderly Patients with Myocardial Infarction and Multivessel Disease" (FIRE) trial will be enrolled patients aged 75 or more with myocardial infarction and multivessel disease. This population represents the one with the worst prognosis and in which PCI procedures are the most challenging. The study randomizes non-culprit lesions (after successful treatment of the culprit lesion) to optimal medical treatment vs. a physiology guided revascularization. Physiology assessment can be performed with any tools. At the end of January 2021, more than 900 patients have been randomized. Around

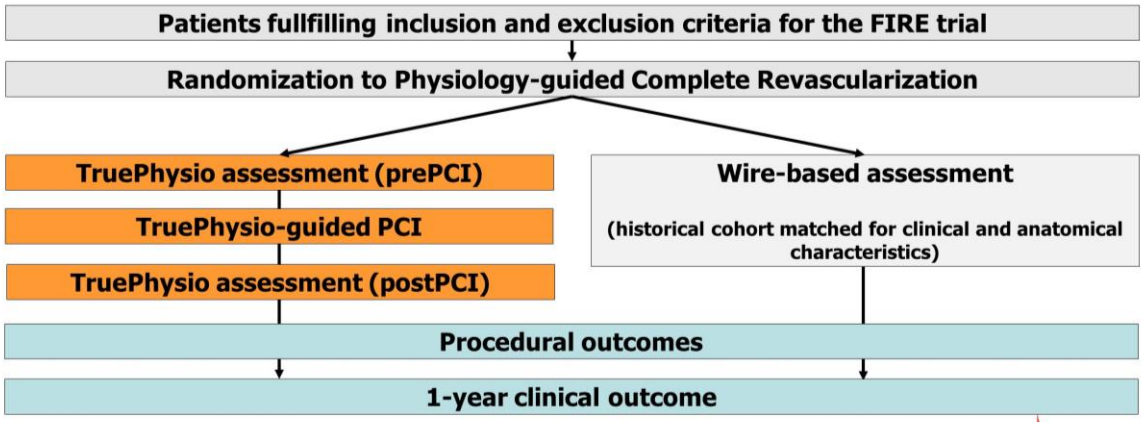
300 patients for a total of more than 380 non-culprit coronary lesions have been investigated with wire-based physiology (40% Comet guidewire, 35% Certus guidewire, 25% Verrata guidewire). These non-culprit lesions show a higher anatomical complexity as compared to previous studies. This is not surprising because in older MI patient severe calcifications, long disease, vessel tortuosity are more common. In addition, the protocol does not exclude ostial lesions or bifurcations, and physiology assessment must be performed also in these conditions. Although not mandatory, the protocol suggests that the physiology assessment is performed at the best of the available evidence, then including pullback in case of long or serial lesions and post-PCI assessment. All these elements clearly explain why the FIRE trial population is the ideal subset for the validation of TruePhysio microcatheter. The use of TruePhysio microcatheter in the remaining patients enrolled in selected centers will permit to test the performance of the device in more than 100 non-culprit lesions at very high complexity. This performance will be compared with that of matched FIRE patients where the assessment has been done with a wire-based technology.

STUDY RATIONALE

TruePhysio microcatheter has been developed to permit physiology assessment of complex lesions and challenging vessels and to facilitate post-PCI assessment. However, its scientific data are only preliminary and obtained in simple lesions in stable patients. Thus, the present study is aimed at testing:

i) In which percentage of patients TruePhysio microcatheter guarantee a full-physio PCI procedure,
ii) If TruePhysio microcatheter reduces, as compared to wire-based technology, procedural time and contrast administration,
iii) If TruePhysio microcatheter increases, as compared to wire-based technology, the number of vessels where PCI procedure is based on pullback trace,
iv) If TruePhysio microcatheter increases, as compared to wire-based technology, the number of vessels where post-PCI assessment is done.

STUDY FLOW CHART



OBJECTIVES

Objective

- *To perform a propensity matched analysis between patients receiving TruePhysio microcatheter-based vs. wire-based physiology guided PCI procedure.*

Endpoints

- *Number of patients receiving a full physiology guided PCI procedure*
- *Number of patients receiving successful pre-PCI physiology assessment*
- *Procedural time*
- *Fluoroscopy time*
- *Contrast amount*
- *Number of patients with drift*
- *Number of patients receiving whole vessel pullback*
- *Number of patients receiving successful post-PCI physiology assessment*
- *1-year occurrence of vessel oriented cardiac event (VOCE, cardiac death, target vessel MI, target vessel revascularization)*

INCLUSION AND EXCLUSION CRITERIA

All FIRE trial population will be included in the propensity score matching.

Patients in the TruePhysio microcatheter arm will be consecutively enrolled in the centers of Ferrara and Reggio-Emilia.

Inclusion Criteria:

1. Patients ≥ 75 years AND
2. MI (STE or NSTE-MI) 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

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

Wire-based FFR evaluation

Wire-based FFR evaluation has been performed in each center according to international guidelines, document consensus and internal protocol. The wire-based technology was that available in the centre. The operator can hypermic or resting indexes at his/her discretion. The protocol suggests investigating the whole vessel with pullback in case di long disease or serial lesions. Post-PCI assessment was suggested but not mandatory.

TruePhysio microcatheter evaluation

Operators will perform physiology assessment with TruePhysio microcatheter according to manufacturer's instructions. The study procedure suggests performing pullback trace in case of long disease or serial lesions. The study procedure suggests performing post-PCI assessment. In case of poor functional result, the operator should identify the location of the drop with pullback and to classify in: i) instent, ii) focal outside stent, iii) diffuse and iv) combination of the previous.

Assessment of Quantitative Coronary Angiography (QCA)

QCA analysis will be performed offline at the independent functional and angiographic core laboratory of the FIRE trial, using the QAngio XA analysis system (Medis Medical Imaging systems). For each lesion, the stented segment and the peri-stented segments (defined by a length of 5 mm proximal and distal to the stent edge) will be analysed, as previously reported [13].

Follow-up

After initial hospital discharge, routine clinic follow-up will occur at 1 month ± 14 days (telephone contact or clinic visit), and at 1 year (clinic visit).

Case Report Form

The FIRE trial has a dedicated case report form (CRF). This CRF is wide and cover all the possible aspects regarding clinical and anatomical characteristics of patients and lesions. The CRF captures several procedural parameters including procedural time, contrast use and X-ray exposition. A blinded and central core-lab will further review all angiograms classifying and describing all the lesion's characteristics and their complexity.

SAMPLE SIZE CALCULATION

No formal sample size calculation can be applied since this substudy is observational [3].

The sample size of the FIRE trial is 1400 patients (see full protocol for details). All 1400 patients will be considered in the propensity matched population. Ferrara and Reggio Emilia are the top recruiting centres in the FIRE trial (more than 200 patients in each centre). We suppose that before the end of the study, the 2 centres can enroll at least 80 patients (around 100 vessels) where physiology assessment can be performed with TruePhysio microcatheter. This will allow to obtain a powered matching versus patients where physiology was performed with wire-based technology.

REFERENCES

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