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: "Comparison between resting 2D speckle tracking analysis and coronary physiology in the identification of non-culprit coronary lesion in multivessel acute myocardial infarction: the ECHO-FIRE study"

Number of registration: *clinicaltrials.gov NCT03772743*
Principal Investigator FIRE Trial*: Simone Biscaglia, MD*
Principal Investigator ECHO-FIRE Study*: Rita Pavasini, 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 prevalence of patients with multivessel coronary artery disease is increasing both in the setting of ST elevation myocardial infarction (STEMI) and in non-ST elevation myocardial infarction (NSTEMI) because of the aging of the population, that leads to more complex, frail and comorbid patients [1]. The analysis and quantification of the degree of coronary stenosis is of paramount importance and a physiology assessment of intermediate coronary lesions represents the gold standard for the identification of lesions deserving revascularization. In particular fractional flow reserve (FFR) represents a well-validated technique to guide coronary intervention by identification of lesion-level ischaemia [3]. Between alternative methods to assess coronary physiology the quantitative flow ratio (QFR) is an angiographically derived FFR measurement recently developed.

Speckle tracking and coronary physiology

At the same time in clinical practice, all patients undergoing coronary angiography because of an acute myocardial infarction (NSTEMI or STEMI), usually are valued with a complete and standardized transthoracic echocardiography. Speckle tracking is an echocardiographic measurement of myocardial deformation (strain). Multilayer speckle-tracking echocardiography allows the analysis of regional myocardial deformation at a layer-specific level. The three layers considered are the endocardial, the epicardial and mid-wall, where the endocardial layer is the more sensitive to ischemia. A previous small study showed that in the setting of stable coronary artery disease, the assessment of resting whole layer and of endocardial longitudinal strain were significantly reduced in left ventricle segments perfused by vessels with a fractional flow reserve (FFR) ≤0.75 and that the whole-layer and endocardial LS had a modest diagnostic efficiency in identifying LV-segments perfused by vessels with an FFR ≤0.75 [4]. This study had some limits: first of all, the sample was very limited, being enrolled only 39 patients. Secondly, the retrospective design of the study. At the same time in patients with NSTEMI previous studies showed that the analysis of whole and multi-layer global longitudinal and territorial strain were significantly reduced in patients with significant and complex coronary artery disease [5]. Endocardial and territorial longitudinal strain were the most affected and overall global longitudinal strain displayed a good diagnostic performance for the prediction of CAD [5-6]. However results were conflicting about the ability of this method in differentiating between significant stenosis and coronary occlusion [5-6]. Also these studies focusing on patients with NSTEMI had some limits related to the limited number of patients enrolled, and also because coronary lesions were estimated only with visual estimation and not with coronary physiology.

Speckle tracking after revascularization

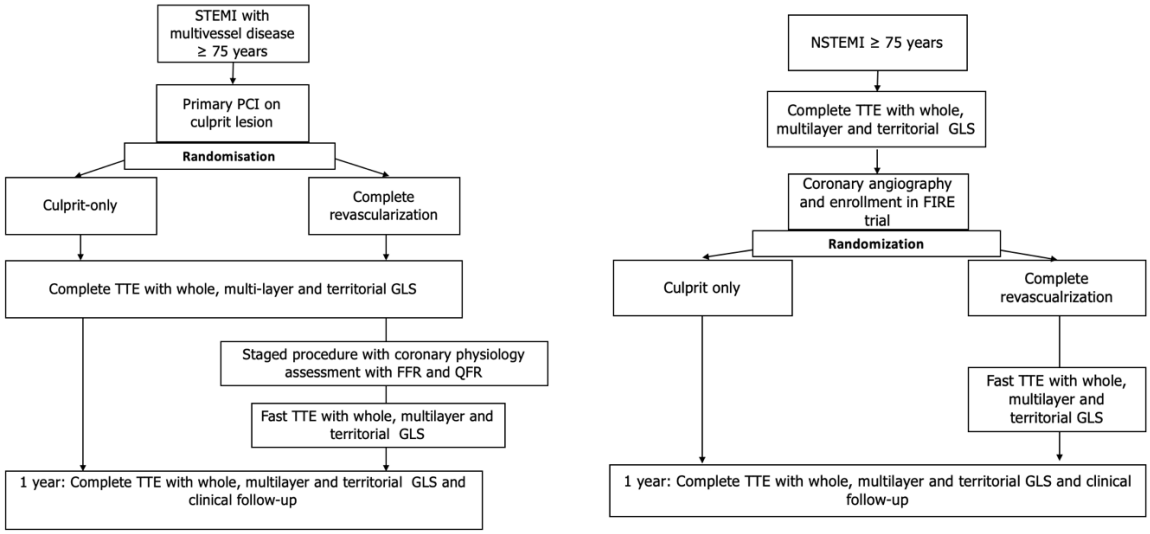
The role of speckle tracking echocardiography has also been valued after revascularization. In particular the combined evaluation of endocardial and epicardial torsion by speckle tracking imaging may be used to differentiate transmural from non-transmural MI after revascularization [7].

Moreover both global and circumferential longitudinal strain showed to be predictors of cardiac events in patients with chronic coronary artery disease [8].

STUDY RATIONALE

At the state of the art there are no data about the relation between FFR and QFR values and speckle tracking parameters (whole layer and multilayer global longitudinal and territorial strain) in patients with NSTEMI and multivessel coronary artery disease or STEMI deserving a staged revascularization procedure.
The FIRE trial is enrolling multivessel patients aged 75 and older with multivessel STEMI and NSTEMI. Coronary lesions will be assessed with coronary physiology, including FFR and QFR. This population represents a perfect scenario to test the relation between the echocardiographic assessment with speckle tracking technique and the coronary physiology.

STUDY FLOW CHART



OBJECTIVES

Primary outcomes

- *Compare the whole, multi-layer and territorial GLS with FFR values of non-culprit coronary lesions in multivessel NSTEMI and STEMI.*
- *Compare the whole, multi-layer and territorial GLS with QFR values of non-culprit coronary lesions in multivessel NSTEMI and STEMI.*

Secondary outcomes

- *To value the prognostic value of whole, multi-layer and territorial GLS in term of rate of device oriented composite endpoint (DOCE, cardiovascular death, target vessel myocardial infarction, clinically driven target lesion revascularization) at 1 year.*
- *To value the prognostic value of whole, multi-layer and territorial GLS in term of rate of the single components of DOCE (cardiovascular death, target vessel myocardial infarction, clinically driven target lesion revascularization) at 1 year.*
- *To evaluate primary outcomes at 3 and 5 years*

INCLUSION AND EXCLUSION CRITERIA

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. Coronary physiology assessment of intermediate lesions with FFR and QFR AND
6. Complete echocardiography performed before coronary angiography in NSTEMI.
7. Signed informed consent

Exclusion Criteria:

1. More than mild valvulopathies
2. Concomitant cardiomyopathies
3. Vessel with previous myocardial infarction
4. Sub-optimal echocardiographic window

STUDY PROCEDURES

All patients enrolled in the FIRE trial ECHO sub-study will undergo transthoracic echocardiography (TTE):

a) In case of STEMI after the primary PCI and before the staged procedure in case of randomization in the complete revascularization arm.
b) The enrollment in the sub-study of NSTEMI patients is subordinate to the presence of a complete echocardiography performed before the angiography. In case of enrollment the patient will undergo echocardiography after the revascularization in case of randomization in the complete revascularization arm.

A fast TTE will be performed after the staged procedure in STEMI patients and after revascularization in NSTEMI of the complete arm.
At 1, 3 and 5 years a complete TTE and a clinical examination will be performed.

Echocardiographic Assessment

All TTE images have to be saved and sent to the central core lab.
For TTE images collection the same rules have to be followed:

- ECG traces have to be recorded.
- Optimized images have to be collected
- For speckle tracking analysis is necessary to adjust depth on left ventricle (LV), with a frame rate of 50-70 MHz.
- Two ECG cycles have to be recorded

The following parameters have to be collected for complete TTE:

- Parasternal long axis view: 2D and color doppler, LVOT diameter.
- Parasternal short axis view: short axis of LV at the basal segments, mid-segments and apex, RVOT diameter and RVOT VTI.
- Four chamber view: 2D and color for both RV and LV, diastolic function assessment with evaluation of mitral inflow pattern (E wave, A wave, deceleration time), Tissue doppler analysis at lateral wall, septum and right ventricle free wall, TAPSE; maximum velocity of TR, image of LV with depth adjusted and FR 50-70 Hz.

- Five chamber view: 2D and color, LVOT VTI, CW VTI.
- Two and three chamber view: 2D and color, image of LV with depth adjusted and a FR 50-70 Hz.
- Subcostal view: IVC

The following parameters have to be collected for fast TTE:

- Parasternal short axis view: short axis of LV at the basal segments, mid-segments and apex,
- Four-three and two chamber view: image of LV with depth adjusted and FR 50-70 Hz.

All measurements will be collected in a specific eCRF.

SAMPLE SIZE CALCULATION

At the state of the art there are no other studies valuing the predictive value of speckle tracking echocardiography in the setting of multivessel coronary artery disease with both STEMI and NSTEMI, and moreover in comparison with a physiology assessment of non-culprit coronary lesions.
For this reason a formal calculation of the sample size is not possible.
Similar study present in the literature are mainly retrospective and based on sample size ranging between 39 and 162 patients (see Table below), with a mean value of 103.
The sample size for the Fire trial is about 1400 patients. Considering the proportion of patients enrolled (aged ≥ 75 years old) that will be excluded because :
of moderate or severe valvular heart disease: 13.5% [9],
of previous MI o concomitant cardiomyopathies [2]: 30%,
of sub-optimal quality of images: 10%,
we estimate to screen at least 525 patients to have a sample size of at least 105 patients, obtaining reliable data.

References	Clinical presentation	Patients	Endpoint
Nishi et al. 2016 [4]	Stable angina	39	Whole layer and endocardial longitudinal strain (LS) are smaller in vessel with FFR ≤ 0.75 (p=0.03)
Sarvari et al. 2013 [5]	NSTEMI	77	Endocardial and territorial LS (TLS) are affected in patients with significant CAD (p<0.001)
Zhang et al. 2016 [10]	NSTEMI	139	Endocardial LS and TLS were closely correlated with Sintax Score value (r=−0.751 and r = −0.753, respectively; P < 0.001)
Liu et al. 2016 [11]	NSTEMI	162	Multilayer GLS is significantly affected in patients with left anterior descending disease (p<0.001)
Shimoni et al. 2011 [12]	NSTEMI and stable CAD	97	Global, segmental and TLS are able to predict CAD (p<0.001)

GLS: global longitudinal strain; LS: longitudinal strain; TLS: territorial longitudinal strain; CAD: coronary artery disease; NSTEMI: non ST elevation myocardial infarction.

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