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: "ClearStent versus Angio-guided Systematic PCI Optimization in the FIRE trial patients" (CLASSY-FIRE)

Number of registration: *clinicaltrials.gov NCT03772743*
Principal Investigator*: 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

Percutaneous Coronary Intervention optimization: when evidence collides with reality

Percutaneous Coronary intervention (PCI) optimization based on imaging or on invasive physiology assessment improves outcome [1], but in clinical practice, it is applied in less than 10% of patients [2, 3]. Reasons for this discrepancy between evidence and practice are manifold. As for physiology assessment, the main limitation is related to its use for stenosis assessment pre-PCI. It is highly unlikely to use physiology as a "pure" post-PCI tool. As for imaging, its use in complex settings is widespread, but due to time and cost constraints, it is applicable in all cases.
For these reasons, less invasive strategies are appealing in the improvement of post-PCI assessment.

Percutaneous Coronary Intervention optimization: trend topic in interventional cardiology: functional assessment

PCI optimization is now one of the hottest topics in the coronary field due to several reasons. The first is the demonstration of a higher than expected rate of suboptimal PCI results in contemporary studies. In the "Physiologic Assessment of Coronary Stenosis Following PCI" (DEFINE PCI) study [4], 500 patients with stable or unstable angina received blinded instantaneous wave free ratio (iFR) evaluation and iFR pullback after angiographically satisfactory result of PCI. In 24% of the patients iFR post-PCI was lower than the iFR threshold for ischemia (≤0.89). In the Angio-based Fractional Flow Reserve to Predict Adverse Events After Stent Implantation (HAWKEYE) trial [5], 602 patients (751 treated vessels) received blinded Quantitative Flow Ratio (QFR) evaluation after successful PCI with second generation drug eluting stent (DES). Authors established the best cut-off for the primary outcome of interest (vessel oriented composite endpoint [VOCE]). The Receiver operating characteristic (ROC) curve analysis identified a post-PCI QFR lower than 0.90 as having the best predictive accuracy for VOCE (AUC 0.77, 95%CI 0.74-0.80, p<0.001, sensitivity 60%, specificity 87%). Based on this threshold, 16% of the vessels had post-PCI QFR <0.90. Patients with post-PCI QFR <0.90 had a higher rate of adverse events (VOCE) during the follow up (25% vs 3.5%, hazard ratio [HR] for VOCE after correction: 2.91, 95%CI 1.63-5.19, p<0.001).
Combining the results of these two studies, around 20% of the patients treated with PCI has suboptimal results. In addition, in DEFINE-PCI authors showed that if all residual focal lesions could be treated with additional PCI, the rate of significant ischemia could be theoretically reduced from 24% to 5%. In HAWKEYE, the functional drop was actionable in 66% of the cases. Issues are often within the stented segment. In the HAWKEYE trial, the pressure drop was located in the stented segment in 13% of patients with post-PCI QFR <0.90, while in the DEFINE-PCI, the pressure drop was in-stent in 38% of the vessel with residual focal disease. However, physiology alone is not able to discriminate the underlying issue, especially in the stented segment, and the application of imaging techniques is not be feasible in all cases.

Percutaneous Coronary Intervention optimization: trend topic in interventional cardiology: imaging

In the "Optical coherence tomography imaging during percutaneous coronary intervention impacts physician decision-making" (ILUMIEN I) study, authors investigated the impact of optical coherence tomography (OCT) on physician decision making and the association with post-PCI FFR values and early clinical events. OCT performed post-PCI led to further procedural optimization in 27% of the investigated lesions, namely in-stent post-dilatation (81%), new stent placement (13%), or both (3%) [6].

ClearStent: an easy to use and informative tool for post-PCI assessment

ClearStent is a enhanced stent visualization (ESV) system allowing a high-quality real-time evaluation during and after stent positioning. It can be useful in the assessment of stent integrity. Images are immediately available and do not require any user interaction. Its main applications are stent fracture and/or stent underdeployment, gap assessment, stent loss, stent thrombosis/in stent restesnosis mechanism evaluation [7-10]. ClearStent can be utilized both alternatively or complementary to more complex intracoronary imaging techniques (intravascular ultrasound [IVUS] or OCT). For instance, in imaging guided PCI, ClearStent can be useful during post-dilation after stenting or during serial stent implantation.

ClearStent: a possible gatekeeper to imaging or further interventions

One of the most interesting applications of this technology has been in stent fracture detection. In a prospective study, ClearStent was systematically employed in the detection of stent fracture in 832 patients with stent fracture predisposing factors. ClearStent was able to detect stent fracture during index PCI. In particular, it was able to detect stent fracture type III and IV in 4.5% of patients. Device oriented composite endpoint was significantly higher in patients with "untreated" type III and IV fractures compared to the "treated" ones (79 vs 9%, $p<0.01$) [10].

FIRE trial: the trial of FIRE for PCI optimization tools

In the "Functional versus Culprit-only Revascularization in Elderly Patients with Myocardial Infarction and Multivessel Disease" 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 optimization tools such as ClearStent may obtain greater results in terms of procedure optimization and prognostic benefit due to the complexity of coronary disease in this subgroup of patients.

STUDY RATIONALE

PCI-optimization through imaging and/or physiology is impactful on prognosis, but largely underutilized. The underlying issue causing suboptimal stent results is within the stented segment in around 20% of the cases. ClearStent utilization post-PCI could represent a simple and easy gatekeeper for imaging or further intervention in the assessment of stented segment, therefore improving the penetration of advanced post-PCI assessment and optimization. Thus, the present study is aimed at testing:

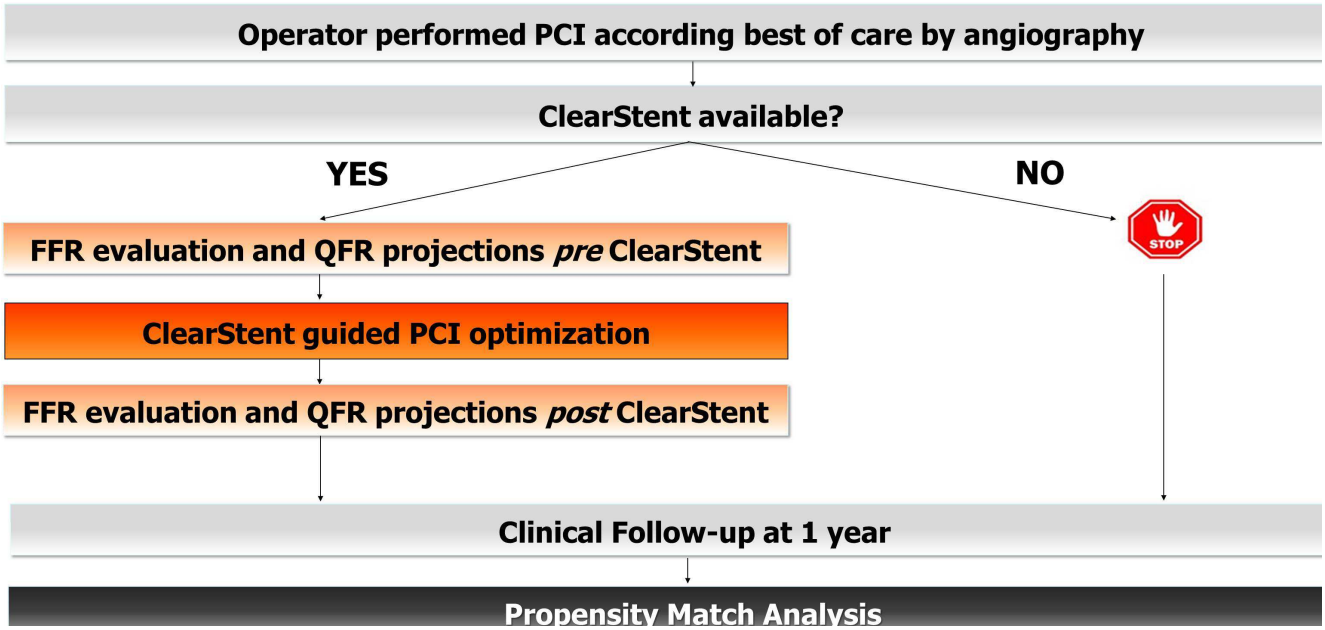
i) In which percentage of patients ClearStent leads to further procedural optimization;

ii) in which percentage of patients a PCI-optimization based on ClearStent is able to improve the final FFR value above the validated threshold that has been demonstrated to correlate with prognosis (>0.86) [1];

iii) in which percentage of patients a PCI-optimization based on ClearStent is able to obtain a ΔFFR ≥0.05 that has been shown as impactful on prognosis [11]

iv) whether ClearStent is able to improve outcome when compared to a matched population of patients receiving optimization as per standard procedure.

STUDY FLOW CHART



OBJECTIVES

Objective in the overall population:

- *To perform a propensity matched analysis between patients receiving or not ClearStent optimization having a Vessel-related Composite endpoint (VOCE) at 12 months as outcome of interest (Cardiac Death, Vessel-related Myocardial infarction, Vessel-related Ischemia-driven revascularization)*

Primary Objectives in the ClearStent arm:

- *To evaluate the rate of Post-PCI ClearStent findings prompting further procedural optimization (in-stent post-dilatation, new stent placement or intracoronary imaging)[6]*
- *To evaluate the percentage of vessels achieving FFR>0.86 after ClearStent optimization [1]*
- *To evaluate the percentage of vessels in which ClearStent Optimization is able to obtain a ΔFFR >0.05 [11]*

Exploratory Objectives in the ClearStent arm:

- *To evaluate if vessel contrast QFR and FFR values are comparable after stenting*
- *To evaluate the percentage of vessels in which ClearStent Optimization is able to improve QFR*
- *To evaluate Minimal Lumen Diameter (MLD) acute gain after ClearStent optimization*

INCLUSION AND EXCLUSION CRITERIA

All FIRE trial population will be included in the propensity score matching.
Patients in the ClearStent arm will be consecutively enrolled in all centers participating to the FIRE trial with ClearStent system availability.

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

FFR evaluation

FFR will be measured with a coronary pressure guidewire at maximum hyperemia induced by intravenous adenosine (140 µg per kilogram of body weight per minute). FFR will be defined as the ratio between the mean distal coronary pressure and the mean aortic pressure, during steady-state maximum hyperemia.

QFR acquisitions

Computation of QFR will be performed offline, using the software package QAngio XA 3D (Medis Medical Imaging System) in agreement with the step-by-step procedure validated in previous studies [5,12]. In the present analysis, we will consider the contrast QFR values. The QFR value will be calculated in the entire vessel, starting from the most proximal available segment until its diameter became less than 1.5 mm. QFR curves of vessels will be analysed and the localization of QFR drop will be classified as: i) instent, ii) focal outside stent, iii) diffuse and iv) combination of the previous. QFR computation will be performed in the functional core laboratory of the FIRE trial [see full protocol for details]. Two independent operators, blinded to outcome, will perform the QFR computation. Both operators are certified operator for QFR computation. The inter-rater agreement between operators will be also evaluated.

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]. The following QCA parameters will be measured: post-procedural MLD, acute gain, acute absolute recoil and maximum footprint. We will evaluate the relationship between optimal ClearStent utilization and these QCA parameters.

ClearStent evaluation

The module and software for the ClearStent images are built into the radiographic system (Siemens Healthcare). A balloon catheter with radiopaque markers is placed in the region of interest to allow registration and processing of all frames within the acquired sequence. Next, 45-60 frames of cine images are obtained at the rate of 30 frames/s, with or without contrast medium injection, with images immediately available on the screen.

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).

SAMPLE SIZE CALCULATION

No formal sample size calculation can be applied since this substudy is observational [6].

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. Based on ClearStent availability in the enrolling centers, expected rate of enrollment, we estimate that at least 500 patients will receive ClearStent evaluation. This will allow to obtain an overall population of matched patients of around 1000 patients.

In addition, considering the data from the ILLUMIEN 1 [6] where 467 lesions were included in the post-PCI analysis, we believe that 500 patients will be sufficient to generate reliable data.

References

1. Agarwal SK, Kasula S, Hacioglu Y, Ahmed Z, Uretsky BF, Hakeem A. Utilizing Post-Intervention Fractional Flow Reserve to Optimize Acute Results and the Relationship to Long-Term Outcomes. JACC Cardiovasc Interv. 2016;9:1022-31.
2. Tebaldi M, Biscaglia S, Fineschi M, Musumeci G, Marchese A, Leone AM, Rossi ML, Stefanini G, Maione A, Menozzi A, Tarantino F, Lodolini V, Gallo F, Barbato E, Tarantini G, Campo G. Evolving Routine Standards in Invasive Hemodynamic Assessment of Coronary Stenosis: The Nationwide Italian SICI-GISE Cross-Sectional ERIS Study. JACC Cardiovasc Interv. 2018;11:1482-1491.
3. Koskinas KC, Nakamura M, Räber L, Colleran R, Kadota K, Capodanno D, Wijns W, Akasaka T, Valgimigli M, Guagliumi G, Windecker S, Byrne RA. Current use of intracoronary imaging in interventional practice - Results of a European Association of Percutaneous Cardiovascular Interventions (EAPCI) and Japanese Association of Cardiovascular Interventions and Therapeutics (CVIT) Clinical Practice Survey. EuroIntervention. 2018;14:e475-e484.
4. Allen J, Late Breaking Trials session at ACC 2019, NCT03084367.
5. Biscaglia S, Tebaldi M, Brugaletta S, Cerrato E, Erriquez A, Passarini G, Ielasi A, Spitaleri G, Di Girolamo D, Mezzapelle G, Geraci S, Manfrini M, Pavasini R, Barbato E, Campo G. Prognostic Value of Quantitative Flow Ratio measured immediately after Successful Stent Implantation: The International Multicenter Prospective HAWKEYE study. JACC Cardiovasc Interv. 2019; In press.
6. Wijns W, Shite J, Jones MR, Lee SW, Price MJ, Fabbiocchi F, Barbato E, Akasaka T, Bezerra H, Holmes D. Optical coherence tomography imaging during percutaneous coronary intervention impacts physician decision-making: ILUMIEN I study. Eur Heart J. 2015;36:3346-55.
7. Biscaglia S, Tumscitz C, Tebaldi M, Andrenacci E, Pavasini R, Campo G, Ferrari R. Enhanced stent visualization systems during PCI: A case series and review of literature. J Cardiol Cases. 2015;12:1-5.
8. Biscaglia S, Campo G, Tebaldi M, Tumscitz C, Pavasini R, Fileti L, Secco GG, Di Mario C, Ferrari R. Bioresorbable vascular scaffold overlap evaluation with optical coherence tomography after implantation with or without enhanced stent visualization system (WOLFIE study): a two-centre prospective comparison. Int J Cardiovasc Imaging. 2016;32:211-223.
9. Biscaglia S, Ugo F, Ielasi A, Secco GG, Durante A, D'Ascenzo F, Cerrato E, Balghith M, Pasquetto G, Penzo C, Fineschi M, Bonechi F, Templin C, Menozzi M, Aquilina M, Rognoni A, Capasso P, Di Mario C, Brugaletta S, Campo G. Bioresorbable Scaffold vs. Second Generation Drug Eluting Stent in Long Coronary Lesions requiring Overlap: A Propensity-Matched Comparison (the UNDERDOGS study). Int J Cardiol. 2016;208:40-5.
10. Biscaglia S, Tebaldi M, Tumscitz C, Pavasini R, Marchesini J, Gallo F, Spitaleri G, Zaraket F, Serenelli M, Cimaglia P, Bugani G, Campo G. Prospective Identification of Stent Fracture by Enhanced Stent Visualization System During Percutaneous Coronary Intervention. Circ J. 2016;81:82-89.
11. Depta JP, Patel JS, Novak E, Gage BF, Masrani SK, Raymer D, Facey G, Patel Y, Zajarias A, Lasala JM, Amin AP, Kurz HI, Singh J, Bach RG. Risk model for estimating the 1-year risk of deferred lesion intervention following deferred revascularization after fractional flow reserve assessment. Eur Heart J. 2015;36:509-15.
12. Spitaleri G, Tebaldi M, Biscaglia S, Westra J, Brugaletta S, Erriquez A, Passarini G, Brieda A, Leone AM, Picchi A, Ielasi A, Girolamo DD, Trani C, Ferrari R, Reiber JHC, Valgimigli M, Sabatè M, Campo G. Quantitative Flow Ratio Identifies Nonculprit Coronary Lesions Requiring Revascularization in Patients With ST-Segment-Elevation Myocardial Infarction and Multivessel Disease. Circ Cardiovasc Interv. 2018;11:e006023.
13. Hioki H, Brugaletta S, Ishida K, Campo G, Biscaglia S, Ortega-Paz L, Cortese B, Varricchio A, Latib A, Sabaté M, Tespili M, Ielasi A. Impact of Absorb bioresorbable scaffold implantation technique on post-procedural quantitative coronary angiographic endpoints in ST-elevation myocardial infarction: a sub-analysis of the BVS STEMI STRATEGY-IT study. EuroIntervention. 2019;15:108-115.