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: "Efficacy and Safety of Supraflex Cruz in Patients with High Dual Risk treated with short DAPT regimen: the FIRE-HDR study"

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

High Dual Risk (HDR) Patients: an emerging and challenging population

In a general acute coronary syndrome (ACS) population, one out of three patients is at high ischemic and bleeding risk according to Global Registry of Acute Cardiac Events (GRACE) and 'Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines' (CRUSADE) score as showed in a recent analysis of 17.701 ACS patients (1). Patients with both high GRACE and CRUSADE score had higher mean age (71.9±11.9) compared to the overall population (65.9±13.1). This subgroup of patients can be defined as high dual risk (HDR) patients (ischemic and bleeding) and it presented also higher risk of in-hospital NACE (10.9% vs 5.5%, HR 6.33 [3.55, 11.29], p<0.001) and 30-day mortality (8.2% vs 4.3%, HR 10.79 [5.33, 21.81], p<0.001). Interestingly, patients in this group received optimal medical therapy (>90% of ACE-I, statin and beta-blocker treatment at discharge), but significantly less coronary artery angiography (62.0% vs 72.3%, HR 0.24 [0.20, 0.29], p<0.001) and DAPT on discharge (74.6% vs 84.3%, HR 0.26 [0.20, 0.34], p<0.001) (1). Whether these patients would benefit from more aggressive management in terms of revascularization and DAPT is unclear and requests further investigations.

New HBR definition

Multiple efforts have been made to improve the treatment of high bleeding risk patients (HBR). Recently, a new and more strict definition of HBR has been suggested by The Academic Research Consortium for High Bleeding Risk (ARC-HBR), a large consensus of expert, in order to be able to focus on patients at real HBR and improve their outcome (2). Bleeding Academic Research Consortium (BARC) 3 or 5 risk of ≥4% at 1 year or a risk of an intracranial hemorrhage (ICH) of ≥1% at 1 year was considered as HBR. Consequently, major criteria are defined as any criterion that, in isolation, is considered to confer a BARC 3 or 5 bleeding risk of ≥4% at 1 year or any criterion considered to be associated with a risk of ICH of ≥1% at 1 year. A minor criterion for ARC-HBR is defined as any criterion that, in isolation, is considered to confer increased bleeding risk, with a BARC 3 or 5 bleeding rate of <4% at 1 year. Patients are considered to be at HBR if at least 1 major criterion or 2 minor criteria are met.

ARC-HBR Major Criteria

- Anticipated use of long-term oral anticoagulation
- Severe or end-stage CKD (eGFR <30 mL/min)
- Hemoglobin <11 g/dL

- Spontaneous bleeding requiring hospitalization or transfusion in the past 6 months or at any time, if recurrent
- Moderate or severe baseline thrombocytopenia (platelet count <100 X 109/L)
- Chronic bleeding diathesis
- Liver cirrhosis with portal hypertension
- Active malignancy (excluding non-melanoma skin cancer) within the past 12 months
- Previous spontaneous ICH (at any time)
- Previous traumatic ICH within the past 12 months
- Presence of a brain arteriovenous malformation
- Moderate or severe ischemic stroke within the past 6 months
- Non-deferrable major surgery on DAPT
- Recent major surgery or major trauma within 30 d before PCI

ARC-HBR Minor criteria

- Age >_75 y
- Moderate CKD (eGFR 30–59 mL/min)
- Hemoglobin 11–12.9 g/dL for men and 11–11.9 g/dL for women
- Spontaneous bleeding requiring hospitalization or transfusion within the past 12 months not meeting the major criterion
- Long-term use of oral NSAIDs or steroids
- Any ischemic stroke at any time not meeting the major criterion

Lack of Evidence-based treatment in HDR patients

There are no trials focused on HDR patients. The only trials available regard older patients. In fact, before the recent ARC definition (2), age itself was considered as a major criterion for HBR. At the same time, all these trials were focused on patients with stable presentation (only ≈35% patients had MI), thus with a low percentage of High Dual Risk (HDR) patients.

Older, as well as HBR, patients are usually excluded from traditional clinical trials. The only evidence on older patient regards stent type and dual antiplatelet therapy regimen.

In the "Drug-eluting stents in elderly patients with coronary artery disease" (SENIOR) trial (3), patients ≥75 years with clinical indication to stent implantation were randomized to a biodegradable polymer drug eluting stent (DES) or to a bare metal stent (BMS). The occurrence of the composite primary endpoint (all-cause mortality, myocardial infarction, stroke, or ischemia-driven target lesion revascularization) was significantly lower in the biodegradable polymer DES arm compared to the BMS arm (68 [12%] vs 98 [16%] RR 0·71, 95%CI 0·52–0·94; p=0·02). The difference in the primary endpoint between the two groups was driven by a statistically significant difference in ischemia-driven target lesion revascularization (TLR). Thus, the preferred stent for the treatment of older patients is considered a biodegradable polymer DES.

In the Zotarolimus-eluting Endeavor Sprint Stent in Uncertain DES Candidates (ZEUS) Study, 1606 patients, who qualified as uncertain candidates for DES, were randomized to a hydrophilic polymer-based, second-generation zotarolimus-eluting stent (ZES) versus BMS. Median age was 74 and 62.5% of patients withdraw DAPT at 30 days with good clinical outcome in the DES arm (2.9% MI rate at 2 year) (4). In the ZEUS trial, 44% of patients had MI at inclusion (4). In the SENIOR trial (3) DAPT regimen ranged from 1 to 6 months. Roughly 50% of patients interrupted DAPT at 1 month with a good clinical outcome in the overall population, although only 36% of patients had MI.

Ultrathin struts DES: the thinner the better

A recent prespecified substudy of the "Comparison of Biodegradable Polymer and Durable Polymer Drug-eluting Stents in an All Comers Population" (BIO-RESORT) trial (5) compared three different DES (thin, very-thin and ultra-thin struts) in patients with at least one small vessel treated. Interestingly, DES with particularly thin struts had the lowest incidence of target lesion revascularization at 3 years. This benefit was confirmed at multivariable analysis.

Supraflex Cruz: an attractive option for HDR patients

Recently, Supraflex Cruz (Sahajanand Medical Technologies Pvt Ltd, Surat, India) received CE-approval. Cruz is a biodegradable polymer-coated sirolimus-eluting stent (SES).

The most relevant novelty of this platform is represented by the ultrathin (60 μm) cobalt–chromium (Co–Cr) struts stent. This ultra-thin strut is available for all the stent sizes differently from its competitors. Moreover, it will probably allow an even shorter duration of DAPT since its struts are the thinnest actually available. This characteristic is particularly important also in light of the results from the BIORESORT study (5).

For the same reason, in another ongoing contemporary trial focusing on HBR patients (Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation With an Abbreviated Versus Prolonged DAPT Regimen [MASTER DAPT], NCT03023020), a thin-strut biodegradable polymer sirolimus eluting stent has been utilized (Ultimaster, Terumo Corporation, Tokyo, Japan). Recently, the results of the "Thin Strut Sirolimus-eluting Stent in All Comers Population vs Everolimus-eluting Stent (TALENT)" all-comers trial" have been published (6). Supraflex was non-inferior to the actual best in class (Xience, Abbott) in terms of device oriented composite endpoint (DOCE) with very low rate of MI (2.5%) and definite or probable stent thrombosis (0.8%). Interestingly, in the per-protocol analysis, Supraflex showed a significant 61% reduction of clinical indicated TLR (3.1 vs. 1.2%, p=0.02). The newer version of the stent (Supraflex Cruz) has a new proprietary Z-link system allowing a better deliverability in complex settings, particularly frequent in HDR patients. Supraflex Cruz™ is the latest generation drug-eluting stent and has received CE mark approval in June-2019 in the European Union. Safety and performance of the Supraflex Cruz™ stent has been supported by early OCT imaging studies (TAXCO and SiBi) which demonstrated low inflammation and very early healing properties. The TAXCO study was designed to compare the degree of neointimal coverage and the prevalence of malapposition at 6 months subsequent to implantation of Supraflex Cruz™ stent and Xience stent using OCT. Total 37 patients were included in the study. Among them, 21 patients had been treated with Supraflex Cruz™ stent and 16 with Xience stent. This OCT study found no significant difference in mean percentage of uncovered struts (1.87±3.86 vs. 2.42±3.45, p=0.137) and malapposed struts (0.05±0.20 vs. 0.21±0.69, p=0.302) at 6 months after implantation of Supraflex Cruz™ stent, when compared with Xience stent. Also, SiBi study was designed to evaluate early phase (4-6 weeks) neointimal coverage after implantation of Supraflex Cruz™ stent using OCT. This study included 25 patients who underwent OCT analysis after 35.3±5 days of Supraflex Cruz™ stent implantation. This study demonstrated that Supraflex Cruz™ stent has an excellent healing profile with a mean of 91.26% strut coverage after 35.3±5 days of the index procedure. Furthermore, Supraflex Cruz™ Multicenter Registry demonstrates the 1-year clinical outcomes of Supraflex Cruz™ stent in patients with coronary artery disease from real-world clinical practice. A total of 1203 patients were included in this registry irrespective of lesion complexity, co-morbidities and acute presentation and the primary endpoint, cumulative events of target lesion failure at 1-year, were noted in 3.8% of patients, which included 0.6% cardiac deaths, 1.3% myocardial infarctions, and 1.9% target lesion revascularizations. Thus, Supraflex Cruz could represent an attractive platform in the treatment of HDR patients thanks to its clinical data and technical characteristics.

FIRE trial: the house of HDR patients

The FIRE trial population will be composed by the patients at the highest ischemic risk, being MI older patients with multivessel disease. In addition, it can be anticipated that at least 50% of the enrolled patients will meet the ARC criteria for HBR since all patients will have at least one minor criteria for HBR. Thus, it represents a unique possibility to generate data on HDR patients in order to improve their treatment.

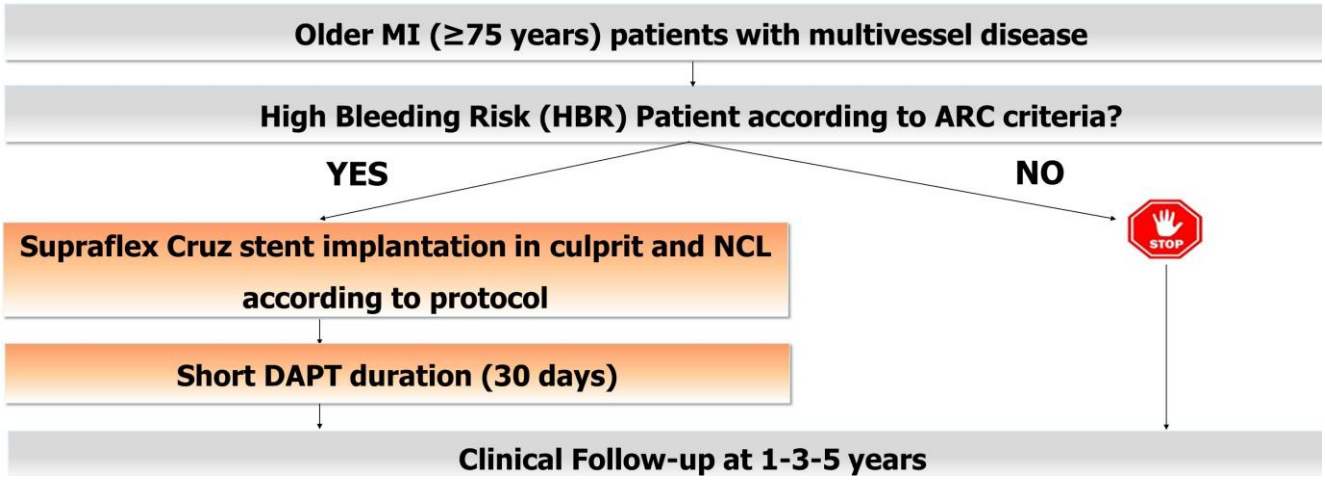
FIRE trial: the trial of FIRE for bioresorbable polymer DES with thin struts

For the same reason, FIRE trial population represents the most challenging setting for a promising platform as Supraflex Cruz.

STUDY RATIONALE

High Dual Risk (HDR) patients are frequent in clinical practice, being at least one third of ACS patients, and they represent the subgroup of patients with the worst prognosis. However, no study has ever been focused on the treatment of this subset of patients, especially taking into account the two competing risk: the ischemic and the bleeding one. Ultra-thin strut stent with bioresorbable polymer seems to be very appealing in this population, also allowing a short DAPT regimen. To date, no platform has been tested in HDR patients. The FIRE trial is the perfect population to generate data on HDR patients. Thus, the present study is aimed at testing the safety and efficacy of sirolimus eluting ultrathin struts biodegradable polymer DES (Supraflex Cruz) in HDR patients treated with short DAPT regimen (1 month)

STUDY FLOW CHART



OBJECTIVES

Primary Objectives:

- *To evaluate the rate of device oriented composite endpoint (DOCE, cardiovascular death, target vessel MI, clinically driven target lesion revascularization) (7) at 1 year in HDR patients treated with sirolimus eluting ultrathin struts biodegradable polymer DES (Supraflex Cruz) and receiving short DAPT regimen (1 month);*
- *To evaluate the rate of device oriented composite endpoint (DOCE) at 1 year in FIRE trial patients treated with sirolimus eluting ultrathin struts biodegradable polymer DES (Supraflex Cruz);*
- *To evaluate the rate of cardiac death and myocardial infarction at 1 year in HDR patients treated with sirolimus eluting ultrathin struts biodegradable polymer DES (Supraflex Cruz) and receiving short DAPT regimen (1 month);*
- *To evaluate the rate of cardiac death and myocardial infarction at 1 year in FIRE trial patients treated with sirolimus eluting ultrathin struts biodegradable polymer DES (Supraflex Cruz);*
- *To evaluate the clinically driven target lesion revascularization rate at 1 year in HDR patients treated with sirolimus eluting ultrathin struts biodegradable polymer DES (Supraflex Cruz) and receiving short DAPT regimen (1 month);*
- *To evaluate the rate of clinically driven target lesion revascularization at 1 year in FIRE trial patients treated with sirolimus eluting ultrathin struts biodegradable polymer DES (Supraflex Cruz);*

Secondary objectives:

- *To evaluate primary objectives at 3 and 5 years*
- *To compare the outcome between HDR patients and non-HDR patients*
- *To evaluate whether functional complete revascularization improve outcomes in HDR patients*

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. **Meeting ARC-HBR criteria (at least one major or two minor)**
6. Signed informed consent

STUDY PROCEDURES

Stent implantation

Patients included in the FIRE-HDR substudy will receive Supraflex Cruz implantation in culprit and non-culprit lesions (if randomized to complete revascularization). Stent implantation will be according to international guidelines. Imaging and post-dilatation are suggested.

DAPT regimen

The suggested DAPT regimen for HDR patients is 1 month, in agreement with recent evidence regarding the negative prognostic effect of a bleeding complication in this high-risk subset of patients.

Follow-up

After initial hospital discharge, routine clinic follow-up will occur at 1 month ± 14 days, at 1-3-5 years (telephone contact or clinic visit).

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