FIRE trial

Functional versus Culprit-only Revascularization in Elderly Patients with Myocardial Infarction and Multivessel Disease

BACKGROUND

Acute myocardial infarction, multivessel disease and age: the 3 determinants of adverse prognosis

Acute myocardial infarction (AMI) is the most frequent clinical presentation in older adults (≥75 years). Registry data shows that up to 65% of patients ≥75 years with AMI has multivessel disease, namely at least one lesion beyond the culprit one with diameter stenosis >50% and located in a coronary artery different from the culprit vessel. Presence of multivessel disease is a marker of worse prognosis. The rate of adverse events, such as death and MI is 3-fold higher in multivessel disease patients if compared to single vessel disease patients. During a 3-5 years follow-up, the number of adverse events related to non-culprit lesions is double than the one related to culprit lesions (*data from SWEDEHEART registry and PROSPECT trial*). These adverse events are even more frequent in older adults reaching a 15-30% incidence at 1 year. Several studies were focused on older adults with AMI in order to optimize their treatment. The main focus of those studies were: optimal dual antiplatelet therapy (DAPT) duration and type of stent. As for DAPT, data is in favour of a short regimen (1-6 months) as it represents the best balance between ischemic protection and reduction of bleeding events. In both LEADERS FREE and ZEUS trials, age was the main criteria for enrollment and it was considered as a marker of high risk of bleeding event. In the ongoing XIENCE 28 study, age ≥75 years is considered a sufficient criteria to prescribe 28 days of DAPT after stent implantation. As for stent type, the recent SENIOR trial showed that biodegradable polymer second generation drug eluting stents (DES) are the gold standard in older adults receiving percutaneous coronary interventions (PCI). These stents clearly outperformed bare metal stents with a low event rate in presence of a short DAPT regimen. Thus, at the present time, we have sufficient data to consider biodegradable polymer DES and short DAPT as cornerstones of the treatment in older adults with MI.
On the contrary, we have no scientific evidence regarding the best treatment strategy to apply in multivessel disease patients. It is not clear whether to prefer a culprit only strategy or if revascularization of non-culprit lesions is associated to a reduction of adverse events.

Treatment options in MI patients with multivessel disease

Culprit lesion treatment with PCI and stent implantation in MI setting is universally agreed as gold standard since it reduces morbidity and mortality.
In the last 10 years, several studies were focused on the treatment of non-culprit lesions. PRAMI, CULPRIT, DANAMI 3 PRIMULTI, COMPARE ACUTE trial tried to assess if a systematic treatment of non-culprit lesions was associated with an improved prognosis if compared to a culprit only strategy. All these studies showed that complete revascularization clearly reduce the risk of repeated revascularizations. However, no study showed a significant impact on death or MI. When pooled in a meta-analysis, we can observe a trend in favour of MI reduction but data cannot be considered as conclusive. In 2019, COMPLETE trial results will be disclosed. In COMPLETE trial, more than 4000 patients were enrolled with consequent power to detect a difference in terms of death and MI. The limits of all the above mentioned studies are that the mean age was around 60 years and that only ST-segment elevated MI (STEMI) patients were included. No study included a

relevant portion of patients ≥75 years nor included no-STEMI (NSTEMI) patients. However, a culprit lesion is identifiable in more than 90% of NSTEMI patients and the issue on their management is similar to the one of the STEMI patients. In addiction, in older adults, clinical presentation is as NSTEMI in more than 70% of the cases. Consequently, it is mandatory to generate solid data on the correct treatment strategy in these patients.

Actual treatment of older patients with MI and multivessel disease

In younger adults (<65 years), in concordance with the solid scientific evidences, it is widespread a complete revascularization strategy. In older adults (≥75 years), also guidelines, in absence of clear data, suggest a case-by-case decision and suggest to consider age as one of the determinants of the final decision (*Class IIa level of evidence C, ESC NSTEMI guidelines*). Both European and American registry data shows clearly that the most frequently applied strategy is the culprit only one, both in STEMI and NSTEMI patients. Also in the LEADERS FREE trial, patients ≥75 years had multivessel disease in 65% of the cases, but in more than 80% of them, treatment was limited to the culprit lesion. In conclusion, the actual gold standard of treatment in older adults with MI and multivessel disease is the culprit-only strategy.

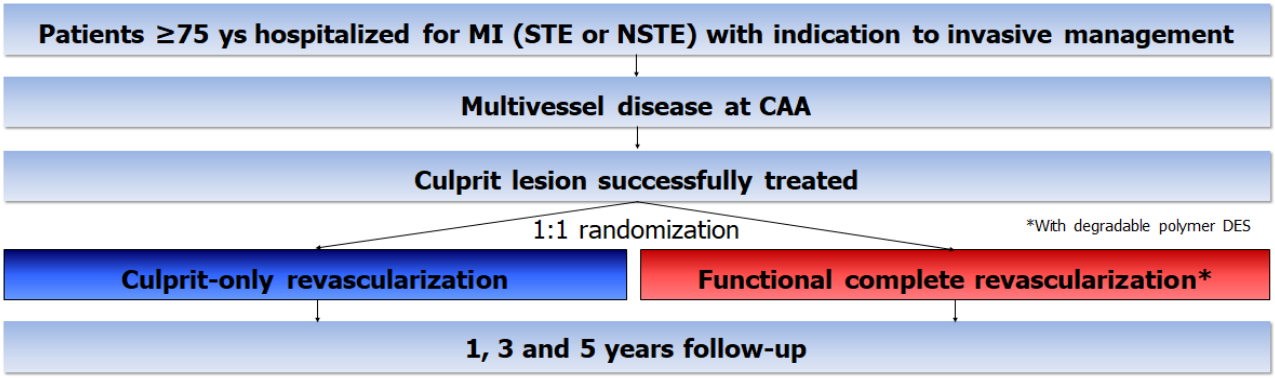
Strategy of complete revascularization and functionally guided complete revascularization

The traditional concept of complete revascularization was based on angiography. Operator visually identified the lesions >50% and decided to treat or not each one of them. Contemporary data on fractional flow reserve and instantaneous free-wave ratio demonstrated that an angio-guided strategy is similar to a coin toss in terms of detection of lesions causing ischemia. This leads to unnecessary PCIs or avoided necessary PCIs in more than 50% of the cases. Studies on angio-complete revascularization probably failed to show an MI reduction because of this reason. In addition, long-term follow-up data of lesions functionally deferred shows that the rate of death and MI at 5 years is below 3%. As a consequence, functional revascularization should be considered as contemporary strategy to achieve a real complete revascularization.

STUDY RAZIONALE

Elderly patients presenting with MI and multivessel disease are the highest risk population with the worst prognosis. No trial has ever been designed to optimize their outcome. The actual real-life standard of care is, in the best of the cases, culprit only revascularization. However, real-life registries show that outcome of ACS elderly patients treated with this strategy is far from being optimal with at least a 15% rate of cardiac death or myocardial infarction at 1 year. To date, studies on this population have been focused on devices (BMS vs biodegradable DES) or on DAPT (long vs short) and no study was focused on evaluating if complete revascularization is able to improve the prognosis in these patients. The contemporary complete revascularization is represented by a functionally-driven revascularization that recently showed to significantly reduce myocardial infarction rate and outperformed an angio-complete revascularization. Thus, our hypothesis is that a functionally-driven complete revascularization in elderly patients with MI and multivessel disease may improve prognosis compared to the actual standard of care in these patients, namely culprit only revascularization. Being a “strategy” trial, we identified the patient-oriented composite endpoint (POCE) as primary outcome of interest (all cause death, any MI, any stroke, any revascularization).

STUDY FLOW CHART



OBJECTIVES

Primary Objective of the Study:

- *To test if a functionally-driven complete revascularization is superior to a culprit only strategy in the reduction of the POCE of all-cause death, any MI, any stroke, any revascularization at 1 year in elderly patients with MI and multivessel PCI.*

Secondary Objectives of the Study:

- *To test if a functionally-driven complete revascularization is superior to a culprit only strategy in the reduction of POCE of all-cause death, any MI, any stroke, any revascularization at 3 and 5 years*
- *To test if a functionally-driven complete revascularization is superior to a culprit only strategy in the reduction of the composite endpoint of cardiovascular death or MI at 1, 3 and 5 years*
- *To test if a functionally-driven complete revascularization is superior to a culprit only strategy in the reduction of all the single components of the POCE and DOCE at 1, 3 and 5 years*
- *To evaluate the rate of ischemic adverse events in patients interrupting DAPT*
- *To evaluate the rate of ischemic adverse events in patients disrupting DAPT*
- *To test if a functionally-driven revascularization is non-inferior to a culprit only revascularization strategy in Contrast-Induced Acute Kidney Injury (CI-AKI) rate*
- *To test if a functionally-driven complete revascularization is superior to a culprit only strategy in terms of quality of life measured with EQ-5D quality of life scale at 1, 3 and 5 years*
- *To test if a functionally-driven complete revascularization is superior to a culprit only strategy in terms of physical performance measured with short physical performance battery (SPBB) at 1, 3 and 5 years*
- *To test if a functionally-driven complete revascularization is superior to a culprit only strategy in terms of angina symptoms control measured with Seattle Angina Questionnaire (SAQ) Frequency scale at 1 year*
- *To test if a functionally-driven complete revascularization is superior to a culprit only strategy in the reduction of ischemia driven revascularization at 1, 3 and 5 years*
- *To test if non-invasive functional strategy based on QFR evaluation is superior to a culprit only strategy in terms of target lesion failure (TLF) at 1, 3 and 5 years*
- *To test if non-invasive functional strategy based on QFR evaluation is superior to a culprit only strategy in terms of ischemia-driven revascularization at 1, 3 and 5 years*
- *To evaluate the rate of adverse events in very high-bleeding risk patients with a 30 days DAPT regimen*

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. Signed informed consent

Exclusion Criteria:

1. Planned surgical revascularization
2. Non-cardiovascular co-morbidity reducing life expectancy to < 1 year
3. Any factor precluding 1-year follow-up
4. Prior Coronary Artery Bypass Graft (CABG) Surgery
5. Impossibility to identify a clear culprit lesion

STUDY PROCEDURES

General Considerations

After coronary artery angiography (CAA) and before randomization, Operator must indicate the culprit lesion and all diseased vessels (based on % stenosis at visual estimation). All patients must be treated with low dose ASA and P2Y12 inhibitor (Ticagrelor unless contraindicated). The use of a glycoprotein IIb/IIIa inhibitor is left to the discretion of the operator. The use of heparin, bivalirudin or low molecular heparin for procedural anticoagulation is also left to the discretion of the investigator. Radial approach is strongly recommended.

Revascularization Strategy

After culprit lesion treatment, the patient will be randomized to one of the two study groups. All patients randomized to culprit only revascularization must not undergo PCI any lesion except from the culprit lesion already treated at the moment of the randomization. Staged procedures are considered protocol violation. These patients must be treated with contemporary guidelines suggested optimal medical therapy in the same way of the patients in the other group.
Patients who are randomized to functional complete revascularization will receive functional assessment on all non-culprit lesions. The system utilized to obtain functional evaluation is left to Operator's discretion. FFR, iwFR, cFFR and QFR are all allowed. PCI is allowed only if functional evaluation is positive according to the threshold of the chosen functional system. PCI of vessel with negative functional evaluation is considered a protocol violation. Routine stress testing and repeat angiography are not indicated in patients whose symptoms are stable.

Criteria for revascularization in patients randomized to the culprit only group

1. *Hospitalization for recurrent MI (STEMI or NSTEMI).*
2. *Hospitalization for hemodynamic instability or refractory ischemic heart failure (defined as Killip class ≥3).*
3. *Intractable angina (CCS Class 3 or 4 symptoms) despite optimal medical therapy and positive functional assessment (FFR, iFR, cFFR, QFR) or objective, proven and documented evidence of ischemia in the territory of one or more vessels (myocardial perfusion scintigraphy with ischemic territory greater than 10% of overall left ventricular mass).*

Follow-up

After initial hospital discharge, routine clinic follow-up will occur at 1 month ± 14 days (telephone contact or clinic visit), 1 year (clinic visit) and yearly clinic visits thereafter up to 5 years.

SAMPLE SIZE CALCULATION

Data regarding death, MI, stroke and revascularization at 1 year in patients ≥75 years with MI and multivessel disease treated with culprit only revascularization are lacking. Taking into account available data (see tables below) and our preliminary data coming from "The frailty in elderly patients receiving cardiac interventional procedures (FRASER) program", we estimated a conservative 15% rate of the primary endpoint at 1 year in the culprit-only strategy group. Considering that functional assessment should reduce the primary endpoint of at least 30% (see table below), 1358 patients are required to have a 80% chance of detecting, as significant at the 5% level, a 30% difference in the primary outcome between the two groups considering a 15% rate of the primary endpoint in the control group. Considering a 2% attrition rate final sample size is inflated to 1400 patients.

Ischemic outcome at 1 year in patients with ACS treated with culprit-only revascularization

Study	MI	Repeat revascularization	MACE
Compare acute	4.7%	17.5%	20.5%
Cvlprit	2.7%	8.2%	21.2%
Prami	8.6%	19.9%	22.9%
Danami-3-Primulti	5%	9%	22%
Translate-ACS	7%	17%	22%

Primary endpoint reduction with functional guided revascularization in ACS setting

Study	Primary endpoint	HR
Compare acute	MACCE*	0.35 [0.22-0.55]
Danami-3-Primulti	all-cause mortality, reinfarction, or ischaemia-driven revascularization	0.56 [0.38-0.83]

*all-cause mortality, nonfatal myocardial infarction, any revascularization, and cerebrovascular events.