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

Statistical Analysis Plan (SAP)

November 8, 2022

Signature page, approval of SAP

I, the undersigned, have read and understand the Statistical Analysis Plan and agree that it contains all necessary information for analyses that will be performed in the trial as set out in this Statistical Analysis Plan, the current version of the World Medical Declaration of Helsinki, ICH-GCP guidelines and the local legally applicable requirements.

Study Principal Investigator

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1 LIST OF ABBREVIATIONS

FIRE trial	"Functional versus Culprit-only Revascularization in Elderly Patients with Myocardial Infarction and Multivessel Disease" trial
MI	Myocardial infarction
MVD	Multivessel disease
NSTEMI	Non-ST segment elevated myocardial infarction
STEMI	ST segment elevated myocardial infarction
POCE	Patient oriented composite endpoint
CV	Cardiovascular
SAP	Statistical analysis plan
TLF	Target lesion failure
DOCE	Device oriented composite endpoint
TVR	Target vessel revascularization
SAQ	Seattle angina questionnaire
EQ-5D	Euro-QoL-5 dimensions
SPPB	Short physical performance battery
DES	Drug eluting stent
eCRF	Electronic case report form
ECG	Electrocardiogram

2 STUDY SYNOPSIS

The “Functional versus Culprit-only Revascularization in Elderly Patients with Myocardial Infarction and Multivessel Disease” (FIRE) trial is a prospective, randomized, multicenter, open-label trial with blinded assessment of outcomes (PROBE trial) comparing functional complete revascularization of non-culprit lesions with culprit-only strategy in patients aged 75 years or more with myocardial infarction (MI) and multivessel disease (MVD). Older patients with MI still suffer from unfavorable prognosis and their prevalence will further increase in the next years. Their clinical presentation is often as Non-ST segment elevation (NSTE) MI and with multivessel disease (MVD). Older patients are usually excluded from clinical trials regarding revascularization strategy that, however, have been conducted only in STEMI setting. Their actual widely utilized strategy is culprit-only treatment. The present study has been designed to evaluate the preferable revascularization strategy in this subgroup of patients, both STEMI and NSTEMI. The objective is to demonstrate that a functionally-driven complete revascularization is superior to a culprit only strategy in the reduction of the patient oriented composite endpoint (POCE) of all-cause death, any MI, any stroke, any revascularization at 1 year in older patients with MI and multivessel disease and in the reduction of the composite endpoint of cardiovascular (CV) death and MI. The sample size of the FIRE trial is 1385 patients.

3 SAP AIM

This statistical analysis plan (SAP) aims to describe in detail the definitions and statistical methods to be implemented for the primary and secondary endpoint analysis in the FIRE trial. Specifically, the plan has the purpose to prospectively define the study populations and endpoints and outline the types of analyses and presentations of data used. The SAP is based on the relevant sections of the FIRE study protocol, version 2, December 12 2019. The objective of the SAP is to maximize the validity and credibility of all study findings by explicitly specifying all data analyses prior to database lock.

4 STUDY POPULATION

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

Exclusion Criteria

1. Planned surgical revascularization
2. Left main as 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

5 OBJECTIVES

5.1 Primary objective

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 older patients with MI and multivessel disease

5.2 Key Secondary Objective

To test if a functionally-driven complete revascularization is superior to a culprit only strategy in the reduction of the composite endpoint of CV death and MI at 1 year in older patients with MI and multivessel disease

5.3 Secondary objectives

- 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 CV death or MI 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 CV death at 1, 3 and 5 years

5.4 Other objectives

The following additional objectives specified in the protocol will be addressed as major sub-projects of this trial program, will be defined in more detail and analyzed later, and will not be included in the main clinical study report:

- 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 evaluate the rate of the device oriented composite endpoint (DOCE) of CV death, MI or target vessel revascularization (TVR)
- To test if a functionally-driven complete revascularization is superior to a culprit only strategy in terms of quality of life measured with EuroQoL 5-Dimensions (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 cost-effective if compared to a culprit only strategy at 1, 3 and 5 years
- To evaluate the rate of ischemic and bleeding adverse events in patients interrupting DAPT

- To evaluate the rate of ischemic and bleeding adverse events in patients disrupting DAPT
- To evaluate the rate of ischemic and bleeding adverse events in high dual risk patients
- To test if a functionally-driven complete revascularization is non inferior to a culprit only strategy in terms of Contrast-Induced Acute Kidney Injury (CI-AKI) occurrence

5.5 Changes of the primary objective during the conduct of the study

No changes of the primary objective will be allowed during the conduct or after completion of the study.

6 STUDY DESIGN

All comers, prospective, randomized, multicenter, open-label trial with blinded adjudicated evaluation of outcomes (PROBE).

6.1 Screening, Allocation and Randomization

All patients undergoing CAA because of MI must be screened for eligibility. Patient's eligibility must be assessed after the evidence of multivessel disease at CAA amenable for PCI with a clear culprit lesion. After eligibility is confirmed, written informed consent must be obtained prior to randomization. Successful culprit lesion treatment must be obtained in all patients before randomization. The suggested stent for culprit lesion treatment is DES with degradable polymer. In STEMI setting, it is possible to enroll the patient also after the successful primary PCI due to the possible difficulty to obtain an informed consent in the setting of STEMI. Key baseline patient characteristics (i.e., inclusion/exclusion criteria, demographics, medical history, details of cardiovascular anatomy, ECG and laboratory test results) will be recorded on the electronic Case Report Forms (eCRF). All CAA from the initial qualifying PCI as well as all functional assessments will be collected and forwarded to an angiographic core lab for further assessment.

Randomization will be performed after CAA and culprit lesion treatment. Randomization will be performed centrally using an internet-based system. The patient identification number (Patient ID) and the treatment allocation will be assigned by the central randomization system. Treatment allocation will be assigned according to a computer generated mixed block randomization list stratified by center, sex and clinical presentation (STE vs NSTE-MI; block sizes: 4 and 6). All patients who are randomized are irrevocably in the study, even if they are subsequently found not to be eligible, or not actually receiving the allocated treatment. Therefore, all patients must be followed until the pre-specified study end date. At the end of the present SAP we report the skeleton flow diagram that will be filled with the actual data.

6.2 Blinding

The trial programme is open-label. Despite the obvious benefits of a double-blind design, it would have been realistically impossible to maintain the blind towards both treating physicians and patients. An independent Clinical Events Committee (CEC) will adjudicate all primary clinical endpoints plus bleedings and stent thrombosis. The committee members and the CEC management team will be completely blinded to the randomized therapy, as well as any patient identifying information. The CEC will adjudicate the events based on pre-determined definitions. The study statistician will be blinded for the interim and primary analyses.

6.3 Definition and assessment of Key Endpoints

The endpoints will be assessed at 1, 3 and 5 years after randomization (primary and secondary objectives). Investigators will record events and the date of the events per patient.

- Primary endpoint: rate of POCE at 1 year

- Key secondary: rate of CV death or MI at 1 year
- Secondary endpoints: rate of POCE at 3 and 5 years
- Rate of CV death or MI at 3 and 5 years
- Rate of CV death at 1, 3 and 5 years

The Clinical Events Committee (CEC) will adjudicate the following events:

- Death
- Myocardial Infarction (MI)
- Stroke
- Transient ischemic attack (TIA)
- Bleeding
- Stent Thrombosis (ST)
- Ischemia-driven Target vessel revascularization (ID-TVR)

This list includes all of the components of the composite primary endpoint as well as other secondary endpoints. The CEC forms are attached at the end of the present SAP.
The functioning rules and the membership of the Adjudication Committee are detailed in the Adjudication Committee Charter before the start of the trial. Adjudication results will be binding for the final analysis.
The rate of events will be calculated for each primary and secondary outcome and compared between treatment groups.

6.3.1 Safety

The following endpoints will be considered to evaluate the safety of functional revascularization:

- Major bleeding according to BARC classification (BARC 3-5)
- Contrast-Induced Acute Kidney Injury (CI-AKI)
- Stroke

6.4 Treatment crossover

Crossover (drop-in and drop-out) is an important feature of the FIRE trial, defined as the following:

- Patients randomized to the OMT alone arm who underwent PCI of a non-culprit lesion not related to protocol criteria for revascularization or

- Patients randomized to the complete revascularization arm who did not receive study PCI of a functionally significant lesion within index hospitalization.

The frequency and percentage of patients who received the assigned treatment and did not crossover will be summarized by treatment group. The frequency and percentage of patients who experienced crossover will be presented, with the reasons, by treatment group. The visit adherence and the proportion of patients who were lost or refused will be tabulated for each visit by treatment group.

6.5 Determination of sample size

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), we hypothesize that the functional assessment should reduce the primary

endpoint by at least 30%. Therefore, the sample size required to have an 80% chance to achieve this result is of 1358 patients, considering as significant the 5% level. Taking into account a 2% attrition rate, the final sample size is inflated to at least 1385 patients (computation by log-rank test). After at least 900 patients have completed the 30-day follow-up, the assumption of the sample size calculation will be checked by estimating the Kaplan-Meier 1-year risk of having reached the primary endpoint. Unadjudicated data will be used for this purpose. No randomization information will be available and all the evaluation on the sample size will be performed in a blinded fashion. If the pooled event rate will be significantly lower than expected, at 0.01 significance level, the sample size may be increased.

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.

		RR reduction				
		27%	**30%**	**33%**	**36%**	**39%**
Power	**90%**	2900	2316	1848	1564	1314
	85%	2478	1980	1578	1336	1122
	80%	2166	1730	1380	1168	982

6.6 Other variables

6.6.1 Socio-demographics/baseline characteristics:

age, gender, height, weight, arterial hypertension, dyslipidemia, current smoker, former smoker, diabetes non-insulin dependent, diabetes insulin dependent, history of ischemic heart disease, prior MI, prior PCI,

history of atrial fibrillation or atrial flutter, COPD, peripheral vascular disease, prior stroke or TIA, prior bleeding, Physical activity at home, Systolic blood pressure (mmHg) at presentation, heart rate (bpm) at presentation, Killip class at presentation, cardiac arrest at presentation, ST segment deviation (both elevation and depression) at presentation.

6.6.2 Laboratory values

White Blood Cell (first value) (u/µl), Haemoglobin (first value) (g/dl), Creatinine (first value) (mg/dl), Creatinine (highest value) (mg/dl), Troponin I/T (peak) (ng/L), CK-MB (peak) (ng/ml), Uric acid (mg/dl), Cholesterol LDL (mg/dl), Glycemia (value at discharge) (mg/dl), Protein (g/dl), Albumin (g/dl)

6.6.3 Procedure-related characteristics:

Date of procedure, access site, procedure duration (minutes), dose of contrast medium (ml), type (brand) of contrast, Dose Area Product (mGy * cm2), complications, number of non-culprit lesions, timing of randomization, lesion(s) segment, type, % stenosis, length, RVD, characteristics (ostial, bifurcation, severe calcifications, severe tortuosity), ACC/AHA classification, number of guidewires utilized, numbers of pre-dilation balloon utilized, number of stent implanted, stent type, diameter, length, post-dilation (yes/no), number of post-dilation balloons, functional assessment tool utilized, value, positive/negative, agreement between treatment and functional value.

6.6.4 Medical therapy at follow-up

Date of eventual withdrawal of aspirin and/or P2Y12 inhibitor, reason of withdrawal, other medications in use: vitamin k antagonist, novel oral anticoagulant, ACE-inhibitor or ARB, beta-blocker, calcium channel blocker, diuretic, statin, Ranolazine, Ivabradine, nitrates, oral antidiabetics, insulin, other.

6.7 Study assessment and follow-up time

After hospital discharge, routine clinic visit follow-up will occur at 1 year and yearly thereafter up to 5 years. At each visit, clinical outcomes, compliance with medical therapy and smoking cessation, will be assessed. LDL, blood pressure and glycemic targets, anginal status (SAQ), quality of life (EQ-5D) and physical performance (SPBB) will be assessed.

variables/ measures /data collected	**Screening**	**Successful culprit PCI**	**In hospital**	**Hospital discharge**	**1 year FU**	**3 years FU**	**5 years FU**
History and Examination	X		X	X	X	X	X
Inclusion/exclusion criteria	X	X					
Informed consent		X					
Randomization		X					
Concomitant medications	X			X	X	X	X
Laboratory exams			X				

POCE				X	X	X	X
Bleedings				X	X	X	X
AE/SAE				X	X	X	X
SPPB			X		X	X	X
SAQ			X		X	X	X
EQ-5D			X		X	X	X
LDL target evalutation					X	X	X
BP target evaluation					X	X	X
Glycemic target evaluation					X	X	X

6.7.1 Follow-up time and censoring

The last follow-up date for each patient is defined as date of death, last study contact, or global study end date, whichever occurs first. The total follow-up time (in days) is defined as time from randomization to the last follow-up date. Day of randomization is counted as Day 1. Survival time for time-to-event (in days) is defined as the date of event, date of death, last study contact, or global study end date, whichever is first, minus date of randomization plus 1. Events that occur before the randomization date will be excluded. Censoring will occur if the patient has been lost to follow-up or has reached the end of the follow-up period without experiencing the primary outcome. All efforts will be made to collect information about the vital status and clinical outcomes for those patients lost to follow-up. In case of no contact, the patient will be censored on their last day of available contact during the study.

6.7.2 Definition of analysis dates

For each patient, the following analysis dates will be determined:

- Randomization date: the date of randomization to functional complete revascularization group or culprit lesion only revascularization group (i.e., OMT alone)
- Event dates for primary, key secondary, and other secondary outcomes (if any)
- Date of death if a patient has died
- Date of last study contact: the date of last known contact with the patient or a third party (including data on patient vital status on records other than follow-up visit CRFs)

For all patients, the global study end date will be defined as the date of the final follow-up visit.

6.7.3 Missing date information

When an event date is not known, the site investigator will be asked to estimate when the event occurred and provide an approximate date based on available information such as date when the patient was last seen or contacted, month, week or season in which event occurred. This information can be meaningfully incorporated into the estimated date recorded, as this is likely to be closer to the true date than any produced by an uninformed computer program.

6.8 Analysis sets and populations

All analyses of co-primary and secondary outcomes, as well as baseline summaries, subgroup analyses will be based on the intention-to-treat (ITT) principle. Sensitivity analyses for the primary and key secondary outcomes will be performed based on the following populations: **Per-protocol population and As-treated population.**

6.8.1 Intention-to-treat (ITT) Population

All patients who are enrolled in the study and randomized to one of the two strategies will be included in the analysis according to the treatment group to which they were assigned, regardless of the treatment they actually received.

6.8.2 Per-Protocol Population

The per-protocol analysis will include the randomized patients who actually received the assigned treatment. Analysis will be performed according to the following groups:

1. Functional Complete Revascularization Strategy:

Patients randomized to Complete Revascularization Strategy who have received Functionally assessment and eventual PCI of the qualifying non-culprit lesion(s) within index hospitalization

2. Culprit Lesion-only Revascularization Strategy:

Patients randomized to Culprit lesion only Revascularization Strategy who have not received PCI of any qualifying non-culprit lesions within index hospitalization.

6.8.3 As-treated Population

The as-treated population will include the randomized patients who actually received a treatment, regardless of the treatment they were assigned. Analysis will be performed according to the following groups:

1. Complete revascularization

- All patients randomized to the *Functional Complete Revascularization Strategy* who have received functional assessment and eventual PCI of the qualifying non-culprit lesion(s) within the index hospitalization

PLUS

- All patients randomized to *Culprit lesion only Revascularization Strategy*, but have received PCI to any of the qualifying non-culprit lesions within the index hospitalization (protocol violation).

2. Culprit lesion only Revascularization

- Patients randomized to *Culprit lesion only Revascularization Strategy* that have not received PCI to any of the qualifying non-culprit lesions within index hospitalization

PLUS

- Patients randomized to *Functional Complete Revascularization Strategy* who have not received PCI to any of functionally significant qualifying non-culprit lesion(s) within index hospitalization.

7 STATISTICAL METHODS

7.1 Statistical team organization

The figures involved in statistical analysis are reported below:

- Coordinators of the Statistics Committee (Dr Elisa Maietti and Prof. Stefano Volpato)
- Executive Statisticians (We4CR Biostatisticians)
- External Statistician (Prof. Giuseppe Biondi Zoccai)

The Executive Statisticians are involved in all the statistical analysis prespecified below, interfacing with the Coordinators of the Statistics Committee for any organizational or technical issue.

The Coordinators of the Statistics Committee are involved in facilitating the communication between Executive Statisticians and Data Managers.

The principal role of the External Statistician is to verify the results at the end of each analysis step.

7.2 Data management and statistical software

Data will be collected on electronic case report forms (eCRFs). The CRF must be signed by the investigator or other appropriate individuals who are authorized by the investigator. Signing of the 'Study completion – Investigator's statement CRF' is considered to be the final authorization of the CRFs. eCRF will be exported into an excel spreadsheet where treatment will be coded to ensure that the study statistician will be blinded for primary analyses. All statistical analyses will be performed using the statistical software R (R core team (2022); URL https://www.R-project.org/).

7.3 Interim analysis

After at least 900 patients have completed the 30-day follow-up, the assumption of the sample size calculation will be checked by estimating the Kaplan-Meier 1-year risk of having reached the primary endpoint. Unadjudicated data will be used for this purpose. No randomization information will be available and all the evaluation on the sample size will be performed in a blinded fashion. If the pooled event rate will be considerably lower than expected the sample size may be increased.

7.4 Data validation and missing values handling

The statistician will perform a plausibility-assessment of variables affecting the analyses on primary and secondary outcomes (randomization date, discharge date, all follow-up dates, all event dates, lost to follow-up and withdrawal; baseline characteristics used to classify patients for stratified analyses).

This is a randomized clinical trial and as such we expect none or a minimal amount of missing data. No imputation of missing values will be performed for the outcomes, rather last available information will be used. Missing values imputation using multiple imputation techniques could be done, in case of any, on covariates (baseline characteristics, laboratory exams, etc….)

7.5 Statistical analysis

Statistical significance will be set at α=0.05 level. Two-sided tests will be done in order to check the superiority of functionally-driven complete revascularization.

7.5.1 Evaluation of demographic, baseline and procedural characteristics

The two treatment groups will be compared with respect to baseline characteristics in order to check that the randomization process has minimized the treatment group differences. Continuous variables will be tested for normal distribution using the Q - Q plot and the Kolmogorov - Smirnov test: normally distributed variables will be summarized as mean ±SD while the other will be summarized as median and inter-quartile range. Differences in the distribution of all continuous variables between the two treatment groups will be investigated with the t test. Categorical variables will be summarized in terms of absolute and relative frequencies and compared using the $\chi 2$ or Fisher exact tests.
If any parameter differs significantly between treatments groups it will be considered as a potential confounding factor in the subsequent analyses.

7.5.2 Primary analysis

To test if a functionally-driven complete revascularization is superior to a culprit only strategy in the reduction of the POCE (all-cause mortality, any MI, any stroke and any revascularization) at 1year, time to first event survival analysis will be primarily done. Survival times > 1 year will be treated as right-censored data. Kaplan – Meyer curves will be estimated to describe survival free from adverse events, and difference between groups will be tested with the log-rank test or Pet-Peto-Prentice test, according to whether or not the hazard functions deriving from Kaplan–Meier estimation will be shown to vary proportionally over time. Subsequently, possible interactions between potential confounding factors and treatments (that is, whether some patient characteristics have an impact on treatment efficacy) will be assessed with Cox regression analysis. Hazard Ratio (HR) along with their 95% CI will be calculated. The assumption of Proportional Harzards (PH) will be checked with Schoenfeld residuals plot and test. In case of PH assumption rejection, an interaction term between the variable and time will be added to the Cox regression model.

In addition to first event analysis, we will assess the composite primary outcome POCE with the use of the Finkelstein–Schoenfeld method, which is based on the principle that each patient in the clinical trial is compared with every other patient in a pairwise manner. The pairwise comparison proceeds in a

hierarchical fashion, using all-cause mortality, followed by frequency of MI when patients cannot be differentiated on the basis of mortality and so on for the other endpoints. This method gives a higher importance to all-cause mortality. We will apply the Finkelstein–Schoenfeld and the win ratio methods (Pocock et al, Eur Heart J 2012) to the patients stratified according to clinical presentation (STE vs NSTE) and number of diseased vessels (2 vs 3), yielding four stratification pools.

7.5.3 Key secondary analysis

To test if a functionally-driven complete revascularization is superior to a culprit only strategy in the reduction of the composite endpoint of CV death and MI at 1 year competing risks survival analysis will be performed. In this analysis time to first event between MI and CV death will be calculated. For those patients not experiencing any MI during the first year, death for cause other than CV will be considered as a competing event. Survival times > 1 year will be treated as right-censored data.

A competing risk regression analysis will be conducted using the Fine and Gray method [Jason P. Fine & Robert J. Gray (1999) A Proportional Hazards Model for the Subdistribution of a Competing Risk, Journal of the American Statistical Association, 94:446, 496-509, DOI: 10.1080/01621459.1999.10474144] to compare the treatment groups. The Cumulative Incidence Function (CIF) for the two treatment groups and the subdistribution hazard ratio (SHRs) with its corresponding 95% CI for composite endpoint event (cause-specific hazard) will be estimated. In addition, if baseline characteristics were differently distributed in the two treatment groups, a multivariable competing risks regression analysis might be performed to take into account any confounding effect estimating the adjusted SHRs for the experimental treatment group.

7.5.4 Secondary analyses

To test if a functionally-driven complete revascularization is superior to a culprit only strategy in the reduction of POCE at 3 and 5 years, the same analysis as reported in paragraph 7.5.2 will be performed. In the evaluation of primary endpoint at 3 years, survival times > 3 years will be treated as right-censored data.

To test if a functionally-driven complete revascularization is superior to a culprit only strategy in the reduction of composite endpoint of CV death and MI at 3 and 5 years, the same analysis reported in paragraph 7.5.3 will be performed. In the evaluation of primary endpoint at 3 years, survival times > 3 years will be treated as right-censored data.

To test if a functionally-driven complete revascularization is superior to a culprit only strategy in the reduction of CV death at 1, 3 and 5 years, a competing risk survival analysis will be performed. In this analysis time to death will be calculated considering CV death as the event of interest and death for any cause other than CV as competing event. The description of competing risk regression analysis has been described in paragraph 7.5.3.

7.5.5 Sub-groups analyses

Sub-group analyses will be performed in order to check whether the treatment was particularly effective in an identified sub-sample of patients. The sample will be stratified according to these subgroups:

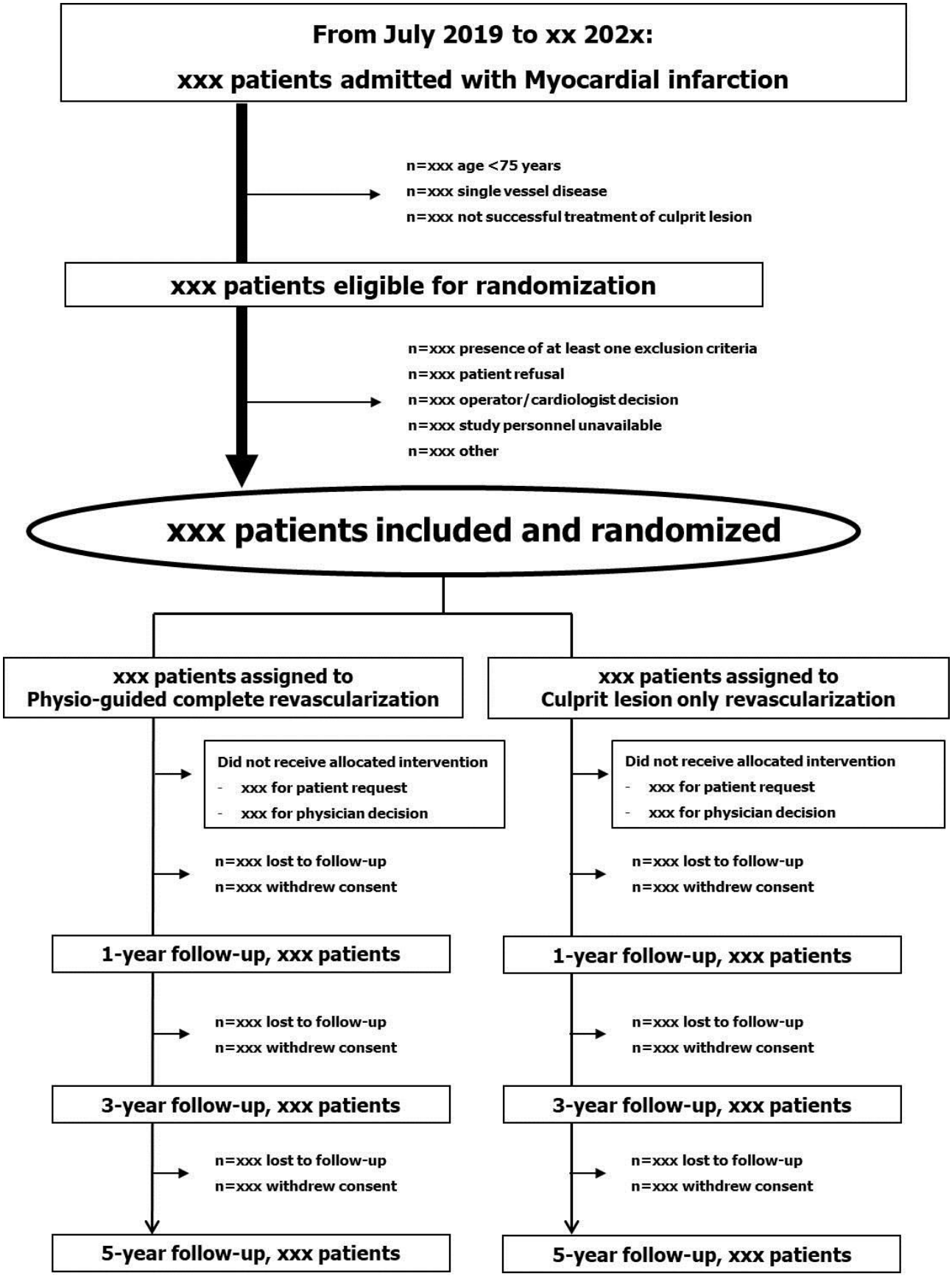
- Patients in whom functional assessment will be obtained with Quantitative Flow Ratio
- Patients in whom functional assessment will be obtained with Resting Indexes

- Patients in whom functional assessment will be obtained with Fractional Flow Reserve
- Patients in whom procedure will be optimized with ClearStent (Siemens, Germany)
- Patients treated with Supraflex Cruz (SMT, India)
- Patients at high ischemic and high bleeding risk treated with Supraflex Cruz and short dual antiplatelet therapy
- Women
- Patients aged 80 or more
- Patients aged 90 or more
- Patients receiving near infrared spectroscopy in one or more vessels
- Patients admitted for ST-segment elevation MI
- Patients admitted for no ST-segment elevation MI
- Patients with non-culprit lesion on left anterior descending
- Patients receiving dual antiplatelet regimen with ticagrelor vs. clopidogrel

Kaplan-Meyer survival curves and HR with 95%CI resulting from univariate comparison between treatment groups will be shown for each subgroup.

A Synopsis of each substudy with detailed description and endpoint will be published on the trial website (www.thefiretrial.com) before the end of the enrollment phase.

8 SKELETON FLOW DIAGRAM



9 CEC forms

9.1 Death

FIRE - CLINICAL EVENTS CLASSIFICATION

Patient ID _____

Adjudicated data: ○ **First adjudication** ○ **Second adjudication** ○ **Third adjudication**

DEATH

1. Date of Death:

Date _____

2. Cause of Death:

A. Cardiac

- ▫ Heart Failure
- ▫ AMI
- ▫ Arrhythmias
- ▫ Valvular Heart Disease
- ▫ Surgical and Non Surgical procedures for Cardiac Disease
- ▫ Other _____

B. Sudden Unexplained Death

C. Vascular

- ▫ TIA - Stroke
- ▫ Aorta
- ▫ Pulmonary Embolism
- ▫ Surgical and Non Surgical procedures for Vascular Disease
- ▫ Other _____

D. Non-Cardiovascular

- ▫ Major Bleeding
- ▫ Cancer Primary Site:
  - ○ Gastrointestinal
  - ○ Prostate
  - ○ Reproductive and renal/urinary tract
  - ○ Lung
  - ○ Brain
  - ○ Breast
  - ○ Melanoma
  - ○ Hematological
  - ○ Other _____
- ▫ Renal Failure
- ▫ Sepsis/Infection
- ▫ Respiratory Failure
- ▫ Other Non CV (specify _____)
- ▫ COVID19 Related

CEC Date _____

E. Unknown

CEC Signature _____

9.2 MI

FIRE - CLINICAL EVENTS CLASSIFICATION

Patient ID _____

Adjudicated data: ○ **First adjudication** ○ **Second adjudication** ○ **Third adjudication**

MYOCARDIAL INFARCTION

○ **SPONTANEOUS MI**

1. Date of MI onset: _____ 2. Hospitalization: □ Yes □ No

3. Universal Definition of MI:
□ Type 1 (Spontaneous)
□ Type 2 (Secondary)
□ Type 3 (Sudden Cardiac Death)
□ Type 4b (Stent Thrombosis)
□ Type 4c (Restenosis)

4. Type:

□ NSTEMI
□ STEMI
□ Unknown

5. Cardiac Markers Available: □ Yes □ No
If Yes,
□ Peak CKMB Value _____ ULN _____
□ Peak Trop. I Value _____ ULN _____
□ Peak Trop. T Value _____ ULN _____

6. Q Wave Classification:
□ Q wave MI
□ Non Q wave MI
□ Unknown (LBBB, paced rhythm, unreadable)
□ No ECG available

7. Coronary Artery Angiography is repeated? □ Yes □ No

○ **PERIPROCEDURAL MI FULFILLING CRITERIA FOR**

□ SCAI definition
□ Type 4a
□ Type 5

Considering available documentation, MI is attributable to

□ LM □ RCA
□ LAD □ GRAFT
□ LCX □ Unknown

CEC Date _____

CEC Signature _____

9.3 Revascularization

FIRE - CLINICAL EVENTS CLASSIFICATION

Patient ID _____

Adjudicated data: ○ **First adjudication** ○ **Second adjudication** ○ **Third adjudication**

NEW CORONARY ARTERY ANGIOGRAPHY AND REVASCULARIZATION

1. Did Coronary Artery Angiography occur?
- ◻ No
- ◻ Yes > Date _____

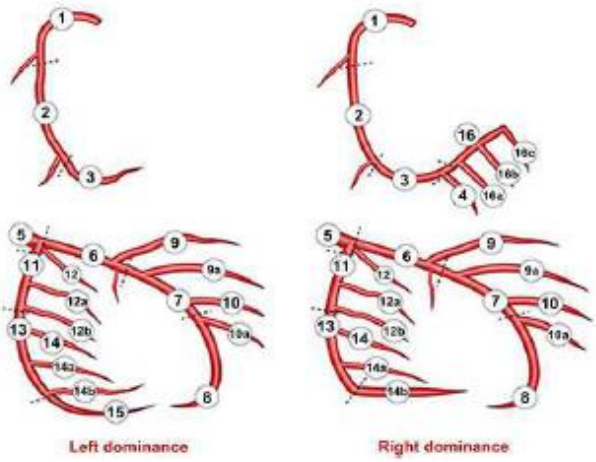
2. Indication?
- ◻ SCAD
- ◻ UNSTABLE ANGINA
- ◻ NSTEMI
- ◻ STEMI
- ◻ OTHER _____

3. Did Revascularization occur?
- ◻ No
- ◻ Yes > Date _____ Indicate vessel/s involved ◻ LM ◻ LAD ◻ LCx ◻ RCA ◻ Graft

4. Type of Revascularization
- ◻ PCI
- ◻ CABG

5a. Is ISR In Stent Restenosis?
- ◻ No
- ◻ Yes > INDICATE SEGMENT

5b. Is ST Stent Thrombosis?
- ◻ No
- ◻ Yes > INDICATE SEGMENT



CEC Date _____

CEC Signature _____

9.4 Cerebrovascular accident

FIRE - CLINICAL EVENTS CLASSIFICATION

Patient ID _____

Adjudicated data: ○ **First adjudication** ○ **Second adjudication** ○ **Third adjudication**

CEREBRO VASCULAR ACCIDENT

1. Date of CVA:

Date _____

2. Type of CVA:

- ▫ Haemorrhagic Stroke
- ▫ Ischemic Stroke
  - o Thrombolysis
  - o Percutaneous Treatment
  - o Medical Therapy
- ▫ Stroke of Uncertain Origin
- ▫ Transient Ischemic Attack
- ▫ Unknown

3. CT Scan available? ▫ Yes ▫ No

If yes please specify below

- o imaging suggestive for intracranial haemorrhage
- o imaging suggestive for subdural haemorrhage
- o imaging suggestive for ischemic area
- o imaging not suggestive for new finding

4. New hospital admission? ▫ Yes ▫ No

If Yes,

Date of Admission _____ Date of Discharge _____

5. CVA leading to:

- ▫ Death
- ▫ Permanent deficit
- ▫ Total recovery

CEC Date _____

CEC Signature _____

9.5 Bleeding

FIRE - CLINICAL EVENTS CLASSIFICATION

Patient ID _____

Adjudicated data: ○ **First adjudication** ○ **Second adjudication** ○ **Third adjudication**

BLEEDING

1. Date of Bleeding:

Date _____

2. BARC Criteria:

- ▫ Type 1
- ▫ Type 2
- ▫ Type 3
  - ▫ 3 A
  - ▫ 3 B
  - ▫ 3 C
- ▫ Type 4
- ▫ Type 5
  - ▫ 5 A
  - ▫ 5 B

3. TIMI Criteria:

- ▫ Major
- ▫ Minor
- ▫ Minimal

4. Location:

- ▫ Vascular access-site
- ▫ Pericardial
- ▫ Genito-urinary
- ▫ Gastro-intestinal
- ▫ Intracranial
- ▫ Intraocular
- ▫ Pulmonary
- ▫ Retroperitoneal
- ▫ Other _____

5. Antithrombotic Agents ongoing at the time of Bleeding:

- ▫ Aspirin
- ▫ Clopidogrel
- ▫ Ticagrelor
- ▫ NOAC
- ▫ Prasugrel
- ▫ Ticlopidine
- ▫ Warfarin

TIMI and GUSTO Bleeding Definitions Developed for Trials of Thrombolytics

TIMI	
Major	ICH Hb drop ≥5 g/dL Hct drop ≥ 15%
Minor	Bleeding: Hb drop ≥ 3 g/dL; Hct drop ≥10% No observed blood loss: Hb drop ≥4 g/dL; Hct drop ≥12%
Minimal	Any clinically overt sign of hemorrhage associated with Hb drop <3 g/dL or Hct drop <9%
GUSTO	
Severe	ICH; bleeding that causes hemodynamic compromise and requires intervention
Moderate	Bleeding requiring transfusion but does not lead to hemodynamic instability
Mild	Bleeding that does not meet criteria for severe or moderate bleeding

Acute Coronary Syndromes — Chesebro JH, et al. *Circulation*. 1987;76:142-154.[3] GUSTO Investigators. *N Engl J Med*. 1993;329:673-682.[4] The Heart.org Medscape

BARC Bleeding Definitions

Type 1	Not actionable, does not cause unscheduled studies, hospitalization, or treatment; may include episodes leading to self-discontinuation of medical therapy
Type 2	Any overt, actionable sign of hemorrhage that does not fit the criteria for types 3, 4, or 5 but does meet ≥1 of the following criteria: (1) requiring nonsurgical, medical intervention; (2) leading to hospitalization or increased level of care; or (3) prompting evaluation
Type 3a	Overt bleeding + Hb drop of 3-5 g/dL Any transfusion with overt bleeding
Type 3b	Overt bleeding + Hb drop ≥5 g/dL Cardiac tamponade Bleeding requiring surgical intervention or IV vasoactive agents
Type 3c	ICH (not including microbleeds or hemorrhagic transformation, does include intraspinal) Subcategories confirmed by autopsy or imaging or lumbar puncture Intraocular bleed compromising vision
Type 4	CABG bleeding
Type 5	Fatal bleeding

Acute Coronary Syndromes — Mehran R, et al. *Circulation*. 2011;123:2736-2747.[5] The Heart.org Medscape

CEC Date _____

CEC Signature _____