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

Version number 2 of the December 12th, 2019

Signature page, approval of Study Protocol

I, the undersigned, have read and understand the protocol and agree that it contains all necessary information for conducting the study for my position in the study and I agree to conduct the trial as set out in this study protocol, the current version of the World Medical Declaration of Helsinki, ICH-GCP guidelines and the local legally applicable requirements.

Study Principal Investigator

_____ _____

Date: Simone Biscaglia, MD

Study Chair

_____ _____

Date: Gianluca Campo, MD

Study Sponsor

_____ _____

Date: Laura Ramaciotti

Investigator Statement

I, the undersigned, have read and understand the protocol and agree that it contains all necessary information for conducting the study for my position in the study and I agree to conduct the trial as set out in this study protocol, the current version of the World Medical Declaration of Helsinki, ICH-GCP guidelines and the local legally applicable requirements.

Site: _____

Address: _____

Principal Investigator: _____

_____ _____

Date: Signature

Table of contents

1 STUDY SYNOPSIS

Study Title:	Functional versus Culprit-only Revascularization in Elderly Patients with Myocardial Infarction and Multivessel Disease (FIRE)
Protocol version:	V2
clinicaltrials.gov	NCT03772743
Date:	December 12, 2019
Study Sponsor:	Consorzio Futuro in Ricerca
Study Principal Investigator:	Simone Biscaglia, MD
Study Chair	Gianluca Campo, MD

2 STUDY ORGANIZATION

2.1 Executive Committee

Simone Biscaglia MD, Gianluca Campo, MD, Matteo Tebaldi, MD, Javier Escaned, MD, PhD, Raul Moreno, MD, PhD, Emanuele Barbato, MD, PhD, Dariusz Dudek, MD, PhD

2.2 Steering Committee

All the PI of the participating centers

2.3 Angiographic and Functional Core Laboratory

Emanuele Barbato, MD, PhD

2.4 Data Safety Monitoring Board

Marco Manfrini, PhD, Carlo Tumscitz, MD

2.5 Clinical Event Committee

Rita Pavasini, MD, Paolo Cimaglia, MD

2.6 Statistics Committee

Elisa Maietti, MSc, Stefano Volpato MD, PhD

2.7 Clinical Project Coordinator

Roberta Piadena, Bs

2.8 Project Coordinator

Veronica Lodolini, Bs

2.9 Data Manager

Elisa Mosele, Bs, Andrea Erriquez, MD

3 BACKGROUND

3.1 Prevalence and Incidence of Myocardial Infarction in elderly patients

Ischemic heart disease (IHD) is the leading cause of death worldwide and its incidence is even higher in elderly patients. The ageing of the population represents a health and socio-economic burden in Western countries and it will soon become a relevant issue also in developing countries (such as China and India). As a consequence, IHD prevalence and impact will further boost. Actual prevalence and incidence of myocardial infarction (MI) in elderly patients (≥75 years) in Western countries range between 15% and 20% with multivessel disease in 55% of the cases (1).

Epidemiology of Myocardial Infarction in Older Patients From the Cardiovascular Health Study

	Age Range (yrs)	Overall	Men	Women
MI†				
Prevalence				
	75-79	13.4	19.2	10.1
	80-84	14.4	21.1	10.2
	85-89	16.5	22.5	12.9
Incidence				
	75-79	12.9	18.3	9.6
	80-84	17.1	24.5	12.5
	85-89	19.5	26.9	14.9

3.2 Guidelines suggested revascularization strategy in elderly patients with MI and multivessel disease

3.2.1 Culprit lesion

Culprit lesion treatment with PCI and stent implantation in MI setting is universally agreed as gold standard since it reduces morbidity and mortality (2).

3.2.2 Non-culprit lesion - STEMI

Non culprit lesion treatment in MI patients is highly debated. Data comes from the ST segment elevation myocardial infarction (STEMI) setting in which an angio-guided complete revascularization seemed to perform better than culprit only treatment with regard to a composite ischemic endpoint of death, MI and target vessel revascularization (3-5). More recent studies compared a functionally-driven vs culprit only

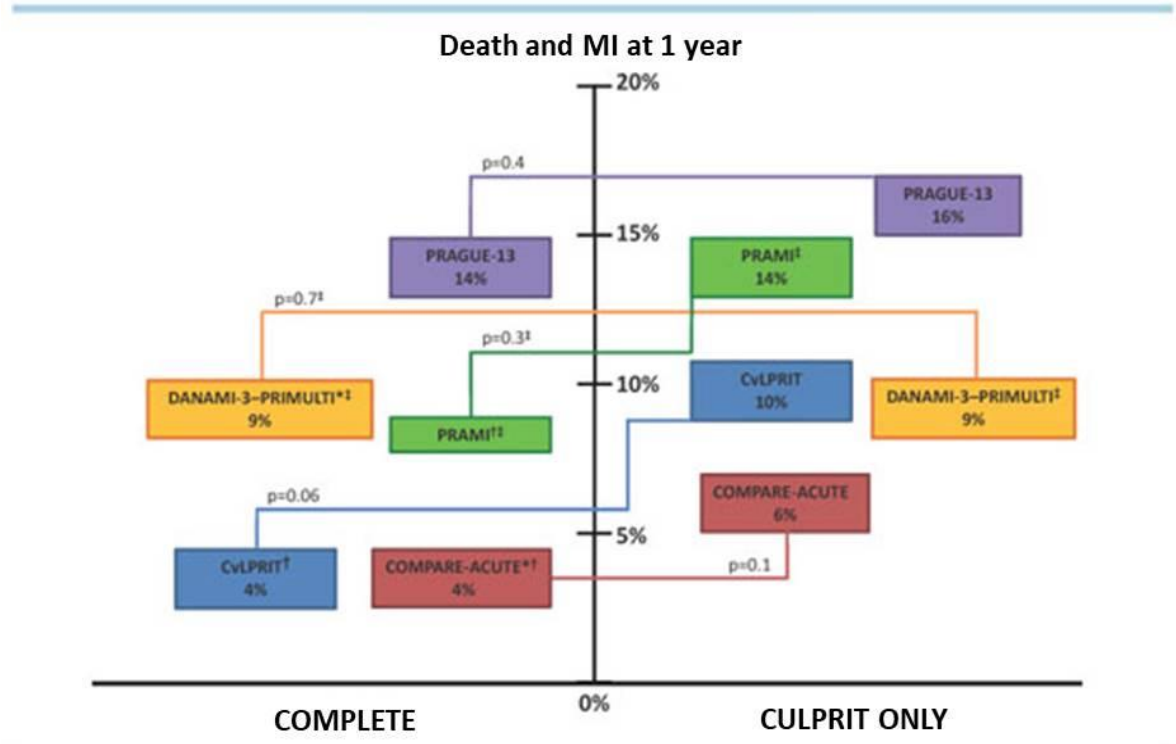
revascularization in STEMI non culprit lesions with similar results (6,7). However, elderly patients are almost non-represented in all the previously mentioned trials since patients' mean age ranges between 60 and 65 years old (see table below). Indeed, <10% trials on MI enrolled patients ≥75 years of age (8).

Mean age in contemporary trials on revascularization strategy in STEMI patients with multivessel disease

Trial	Groups	Mean Age
PRAMI	angio-complete vs culprit only	62
CvLPRIT	angio-complete vs culprit only	65
PRAGUE-13	angio-complete vs culprit only	NA
DANAMI-3 PRIMULTI	FFR complete vs culprit only	63
COMPARE-ACUTE	FFR complete vs culprit only	61

In addition, none of these studies showed a significant reduction in death and MI rate between the two arms.

Death and MI rates in contemporary trials on revascularization strategy in STEMI patients with multivessel disease



The Complete vs Culprit-only Revascularization to Treat Multi-vessel Disease after Primary PCI for STEMI (COMPLETE) trial (ClinicalTrials.gov, identifier: NCT01740479) already ended its enrollment phase and it will

give a definitive answer on the proper revascularization strategy in STEMI patients since its hard primary endpoint (death, MI).

3.2.3 Non-culprit lesion - NSTEMI

There are actually no randomized studies on hard outcomes focusing on the best revascularization strategy in patients with non ST-elevated (NSTE) MI and multivessel disease. In addition, findings from registries and meta-analysis are conflicting (9, 10). On one side, a recent meta-analysis, suggested no clear major adverse cardiac event (MACE) reduction or mortality benefit from complete revascularization (11). On the other end, another recent retrospective British registry enrolled 21.857 patients with NSTEMI and multivessel disease showed a significant reduction in mortality in patients receiving complete revascularization compared to those receiving culprit only strategy confirmed at multivariable analysis and propensity matching (10). However, mean age of the overall population was 68 years old and the findings are merely observational.

The only small randomized trial was focused on the timing of the revascularization. The Single-Staged Compared With Multi-Staged PCI in Multivessel NSTEMI Patients (SMILE) trial compared multivessel PCI during index procedure versus staged multivessel PCI with the former performing better than the latter (12). The Fractional flow reserve vs. angiography in guiding management to optimize outcomes in non-ST-segment elevation myocardial infarction (FAMOUS–NSTEMI) randomized trial randomized NSTEMI patients to functional- versus angio-guided revascularization (13). Fractional flow reserve (FFR) was associated with a lower rate of coronary revascularization compared with angiography-guided management with a slight increase in costs (14). Importantly, the study was not powered for clinical endpoints.

Recently, a minimal approach with second generation drug eluting stent (DES) and short dual antiplatelet therapy (DAPT) regimen has been hypothesized as standard of care in elderly patients although both studies on this topic have the relevant caveat of including more than 50% of patients with stable coronary artery disease (SCAD) (15,16). The important finding of these studies is the paramount impact of bleeding events in this subset of patients. In the absence of randomized data, International Guidelines suggest a single-patient tailored approach with the suggestion to pursue complete revascularization when feasible

(17). However, older and frail patients are less likely to receive complete revascularization as well as guidelines suggested treatments (18). On the contrary, retrospective data hypothesized that a culprit only strategy with DES could be better in octogenarians with multivessel disease (19). In conclusion, at the present time, NSTEMI elderly patients' treatment is highly variable and non-evidence based. In fact, the recent European Guidelines on coronary revascularization (20) recognized a relevant gap in evidence in the treatment of NSTEACS: "In the setting of NSTE-ACS, there are no dedicated prospective studies on the revascularization strategy with multivessel disease. Thus, current recommendations on the choice of lesions to be treated and treatment modality (PCI or CABG) are based on an analogy to findings obtained in SCAD or STEMI. Likewise, the prognostic role of FFR and instantaneous wave-free ratio (iwFR) in guiding myocardial revascularization needs additional clarification."

3.3 Real-life revascularization strategy in ACS elderly patients with multivessel disease

It could be easily anticipated that real-life revascularization strategy in elderly patients with MI and multivessel disease differs from the guidelines suggested one. First of all, real life data shows that elderly patients are significantly less likely to receive guideline-indicated care, including coronary artery angiography (CAA) and percutaneous coronary intervention (PCI), especially in MI setting (rates range from 6.7% to 43.7% vs. from 30.4% to 69.5% in frail and non-frail patients respectively) (21).

In the French Registry of Acute ST-Elevation or Non–ST-Elevation Myocardial Infarction (FASTMI) registry, patients medically managed were stratified according to the performance of coronary artery angiography (CAA) and extent of coronary disease. Interestingly, age was the main determinant of CAA avoidance (76% of patients not receiving CAA were ≥75 years). The two main determinants of mortality in the study population were CAA avoidance and multivessel disease (77% of patients not receiving CAA died at 5 years).(22)

FAST-MI registry outcome data according to performance of coronary artery angiography and extent of coronary disease

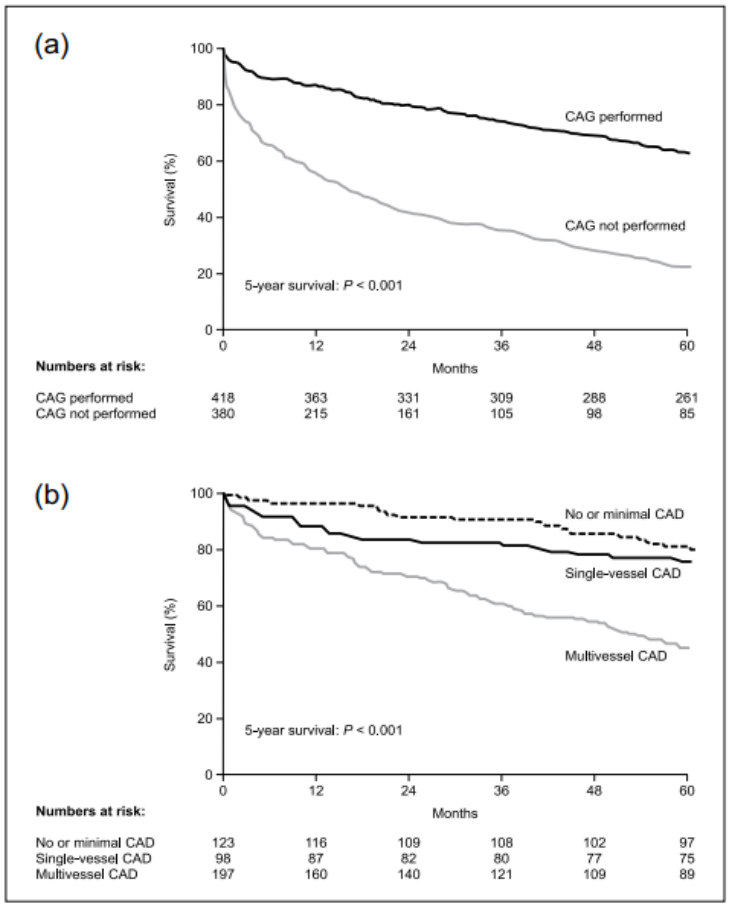


Figure 2. Kaplan–Meier survival curves up to five years according to the performance of coronary angiography (CAG) during the index hospitalization and the extent of coronary artery disease (CAD).

At the same time, PCI decreases in-hospital mortality in MI patients regardless of age, sex, and presence of ST elevation, diabetes mellitus (DM) and chronic kidney disease (CKD) (3).

In a large real-life registry cohort of more than 50.000 ACS elderly patients (≥65 years) from the Medicare database, multivessel disease was present in more than half of the cases (23). Again, elderly patients were largely undertreated according to guidelines suggestions, since 80% of the study population received only culprit lesion treatment at the time of index PCI.

The widespread management of this high risk subset of patients is culprit only revascularization even in randomized trials. In the LEADERS FREE (A Prospective Randomized Comparison of the BioFreedom Biolimus A9 Drug Coated Stent versus the Gazelle Bare Metal Stent in Patients With High Risk of Bleeding) trial (24) high-bleeding risk patients were enrolled (64% presented age≥75 years as inclusion criteria). The 2

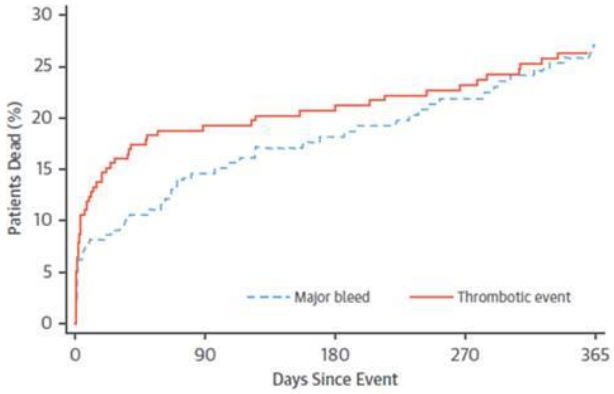
year results showed an occurrence of both ischemic and bleeding events higher than expected (Death 14%, MI 10%, BARC 2-5 18% in the overall population). Age was the main determinant of both ischemic and bleeding events (ischemic event: HR 1.56, 95%CI 1.23–1.97, p<0.001; bleeding event: HR 1.52, 95%CI 1.13–2.06, p<0.001) while multivessel disease was associated with ischemic events (HR 1.66, 95%CI 1.27–2.18, p<0.001). In addition, both ischemic and bleeding events were highly correlated with mortality in 1 out of 4 patients (see Figure below).

TABLE 2 Multivariate Correlates of Primary Safety Endpoint and Major Bleeding

	HR (95% CI)	p Value
Primary safety endpoint*		
Age >75 yrs	1.56 (1.23-1.97)	<0.001
Hemoglobin (per 1 mmol/l <9)	1.32 (1.19-1.46)	<0.001
Congestive heart failure at baseline	1.61 (1.23-2.11)	0.001
Multivessel disease at baseline†	1.66 (1.27-2.18)	<0.001
Number of stents implanted (per additional stent)	1.13 (1.04-1.23)	0.005
BMS	1.28 (1.03-1.59)	0.027
Major bleeding event‡		
Age >75 yrs	1.52 (1.13-2.06)	0.006
Hemoglobin (per 1 mmol/l <9)	1.73 (1.52-1.96)	<0.001
Serum creatinine >150 μmol/l	1.58 (1.10-2.27)	0.012
Planned OAC use post-PCI	2.01 (1.51-2.68)	<0.001

*Primary safety endpoint: composite of cardiac death, myocardial infarction, and definite/probable stent thrombosis. †Multivessel disease includes patients with site-reported 2- or 3-vessel and/or left main disease. ‡BARC bleeding score 3 to 5.
BMS = bare-metal stent(s); CI = confidence interval; HR = hazard ratio; OAC = oral anticoagulants; PCI = percutaneous coronary intervention.

FIGURE 2 1-Year Mortality Following a Major Bleed or a Coronary Thrombotic Event



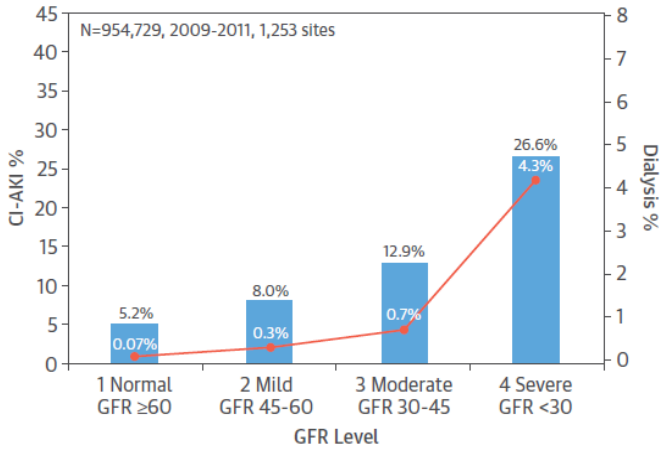
Kaplan-Meier time-to-event curves show the cumulative percentage of patients who died within 1 year following a major bleed or a thrombotic event throughout the 2-year study period.

Interestingly, authors noted that ischemic events could be related to the fact that 62% of patients had multivessel disease while only 22% of patients received multivessel revascularization.

Reasons for this relevant discrepancy between guidelines and real-life data are lack of data and physician's fear of periprocedural and bleeding complications in elderly patients. Moreover, a recent study showed the possible drawbacks of multivessel intervention in elderly patients (25). Authors performed a propensity score matching from a population of 121.588 STEMI patients receiving single or multivessel intervention. The rate of postprocedural complications was higher in patients who underwent multivessel PCI (8.56% vs 7.7%, p <0.001) as well as the length of stay (3.71± 0.02 vs 3.52± 0.01 days, p <0.001) and hospitalization costs ($25,594±109 vs $21,078±43, p <0.001) even after multivariate adjustment. Interestingly, age (hazard ratio (HR) 1.05, 95% confidence interval (CI) 1.04-1.05, <0.001), female gender (HR 1.44, 95% CI 1.29-1.61, <0.001), and a higher burden of baseline co-morbidities (HR 3.29, 95% CI 2.90-3.72, <0.001) were significant

predictors of postprocedural mortality. Noteworthy, age (HR 1.01, 95% CI 1.01-1.01, <0.001) and higher baseline burden of co-morbidities (CCI≥3; HR 1.17, 95% CI 1.11-1.23, <0.001) were important predictors of multivessel PCI. Importantly, the rate of FFR use was 0.34% in the overall population. Moreover, recent studies showed the prognostic impact of periprocedural MI and contrast-induced-acute kidney injury (CI-AKI) in large cohorts of patients (26,27). Elderly patients are more prone to have kidney failure and thus they are at higher risk for CI-AKI and this could be a relevant drawback of complete revascularization in this subset of patients. Studies have consistently reported higher rates of virtually every complication after PCI in those who experience CI-AKI (28). Direct complications of CI-AKI can include volume overload and hyperkalemia that require urgent dialysis, the development of end-stage renal disease, and death. However, CI-AKI is a clinical marker for individuals who are frailer, and susceptible to medical and procedural complications. In the report from the Cath-PCI registry, the rates of recurrent MI, major bleeding, and death in those not on dialysis, and with no evidence of CI-AKI after contrast administration were 2.1% MI, 1.4% bleeding, 0.5% death. These outcomes were all significantly higher in those with CI-AKI (3.8% MI, 6.4% bleeding, 9.7% death) and considerably greater in those with AKI requiring dialysis (7.9% MI, 15.8% bleeding, 34.3% death).

FIGURE 1 **Incidence of CI-AKI and New ESRD Requiring Dialysis From the ACC Cath-PCI Registry**



Incidence of CI-AKI and new ESRD after coronary angiography with PCI according to baseline renal filtration function. Adapted with permission from Tsai et al. (2). ACC = American College of Cardiology; CI-AKI = contrast-induced acute kidney injury; ESRD = end-stage renal disease; GFR = glomerular filtration rate; PCI = percutaneous coronary intervention.

In conclusion, actual real-life strategy in elderly patients with MI and multivessel disease is represented by culprit only revascularization in the best of the cases, while a relevant portion of patient do not receive even CAA.

3.4 Prognosis of elderly patients with MI and multivessel disease

Elderly patients with MI and multivessel disease have an unfavorable prognosis (see table below). Data coming from real-life registries and trials shows mortality rates at 1 year ranging from 10 to 46% according to age and presentation while MI rates at 1 year range from 6 to 14%. Of note, most of the patients enrolled in these studies received culprit only revascularization.

1-year outcome of ACS elderly patients with and without multivessel disease

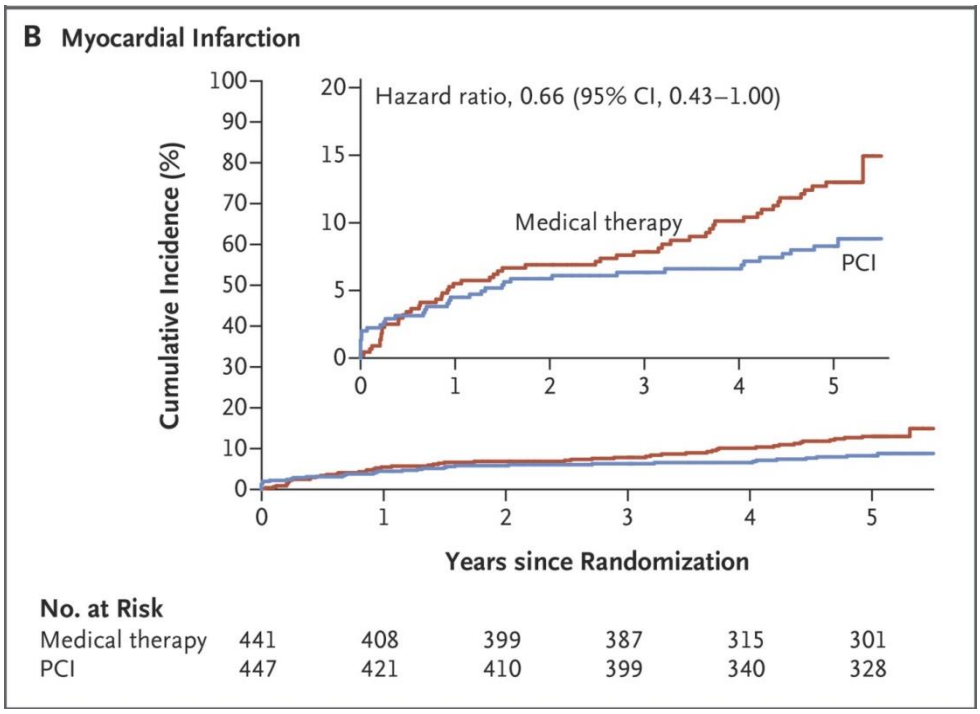
Study	Clinical presentation	Patients no	Death	MI	Death/MI
FRASER	ACS ≥75 MVD	204	10%	6%	16%
CathPCI	ACS ≥65 MVD	50632	11%	/	/
ACUITY	NSTEACS MVD*	609	3%*	13%	16%
Katowice–Zabrze	ACS > 70**	563	7%	6%	13%
CRUSADE	NSTEMI 65-79	21586	13%	9%	22%
CRUSADE	NSTEMI 80-84	7324	24%	12%	36%
CRUSADE	NSTEMI 85-89	5007	34%	14%	48%
CRUSADE	NSTEMI > 90	2794	46	14%	60%

* mean age 62 (upper limit 71); ** 78% unstable angina

3.5 Functionally guided revascularization and prognosis

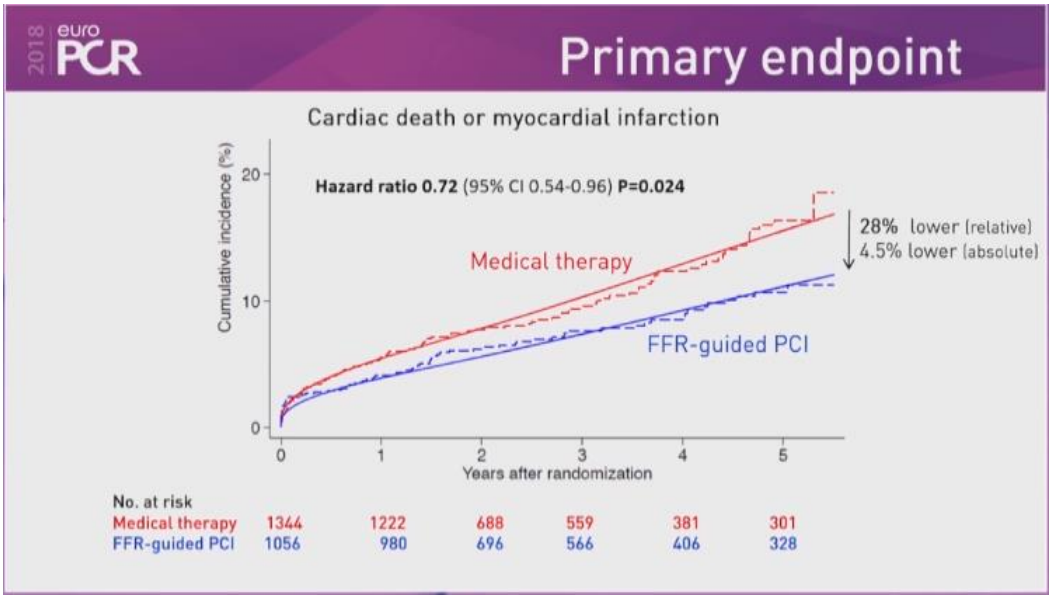
Functionally guided revascularization could improve prognosis in elderly patients with MI and multivessel disease. In fact, 5-year follow-up results of the FAME II trial have been recently published (29). FFR reduced the rate of myocardial infarction by 34% (hazard ratio (HR) 0.66; 95% CI 0.43-1.00) at the 5-year follow-up compared to medical therapy alone (see figures below) with a significant reduction of spontaneous MI (p=0.04, HR 0.62, 95% CI 0.39-0.99).

FAME II 5 years results: all MI



In addition, a patient level pooled analysis of FAME-2, DANAMI-PRIMULTI and COMPARE-ACUTE trials showed a significant 28% reduction of the composite endpoint of cardiac death and MI in the FFR group compared to the medical therapy group (HR 0.72, 95% CI 0.54-0.96, p=0.024) driven by a 29% reduction in MI (HR 0.71, 95 % CI 0.51-0.97, p=0.03, see figures below). The median follow-up was 35 months (interquartile range 12-60 months).(30)

Pooled patient-level analysis of FAME-2, DANAMI-PRIMULTI and COMPARE-ACUTE trials (Zimmermann F, Oral presentation EUROPCR 2018)



In conclusion, functional revascularization may be able to improve prognosis through the reduction of MI. This could be particularly relevant in elderly patients given their higher rate of adverse event. However, patients' complexity and comorbidities as well as procedural lengthening and adenosine side effects contribute to a low adoption of functional evaluation, especially in elderly patients. Moreover, some studies questioned the feasibility of FFR (the most used functional assessment tool worldwide) in MI patients due to microvascular dysfunction (31). Elderly patients have higher probability of microvascular impairment and, thus, are frequently excluded from functional evaluation, especially in MI setting, although no study ever showed a lower benefit from functionally driven revascularization for elderly patients.

In addition, even a target lesion revascularization (TLR) during follow-up is associated with poorer prognosis. A recent pooled patient-level analysis from 21 randomized trials included 32.524 patients who were stratified according to TLR occurrence or not during follow-up. During a median follow-up of 37 months, 2.330 (7.2%) patients underwent a non-emergent, uncomplicated TLR procedure. After adjusting for potential confounders, TLR was an independent predictor of mortality (HR 1.23, 95% CI 1.04 to 1.45; p = 0.02). Patients undergoing non-emergent, uncomplicated TLR had significantly higher rates of non–procedure-related MI compared with those without TVR. Among patients undergoing elective TLR, MI occurring after TLR was an independent predictor of mortality (HR 3.82; 95% CI: 2.44-5.99; p < 0.0001). (32)

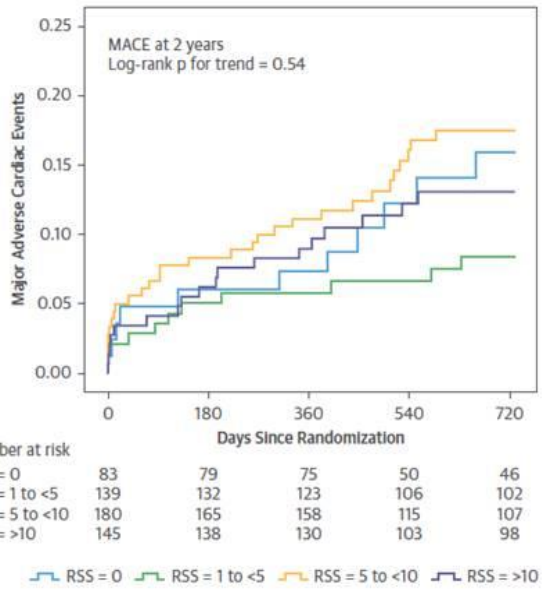
In conclusion, given all the above mentioned data, functional revascularization should be considered the actual standard of care to achieve a real "complete" revascularization.

3.6 Shifting from Angio to Functional complete revascularization

Beyond the already presented clinical data, the paradigm shift from angio to functional complete revascularization is well documented by the Residual SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) score (RSS) paradox. While higher RSS has been associated with worse outcome in patients undergoing angiography-guided PCI, in patients achieving complete functional revascularization, RSS is not related to long term outcome (33) (see Figure below): This elegant subanalysis from the DANAMI-3-PRIMULTI, FAME, and FAMOUS-NSTEMI trials shows once again how the

oculostenotic reflex performs just a little better than a coin flip (HR for MACE 1.01, 95% CI 0.98-1.05, p=0.46).

FIGURE 2 Kaplan-Meier Curves at 2 Years Stratified By the RSS Subgroups



Similar 2-year outcomes were observed among the RSS subgroups, in which an RSS = 0 represents angiographically complete revascularization **(blue line)**. Note that the **blue line** (RSS = 0) and the **purple line** (RSS = >10, the highest RSS subgroup) are superimposed in this figure. MACE = major adverse cardiac event(s); RSS = residual SYNTAX score.

TABLE 3 Unadjusted Hazard Ratios of the RSS for Outcomes at 2 Years

	Unadjusted HR	95% CI	p Value
MACE	1.01	0.98-1.05	0.46
Death	1.02	0.94-1.11	0.67
Myocardial infarction	1.02	0.96-1.08	0.60
Repeat revascularization	1.01	0.96-1.07	0.66
Death or myocardial infarction	1.02	0.97-1.07	0.47

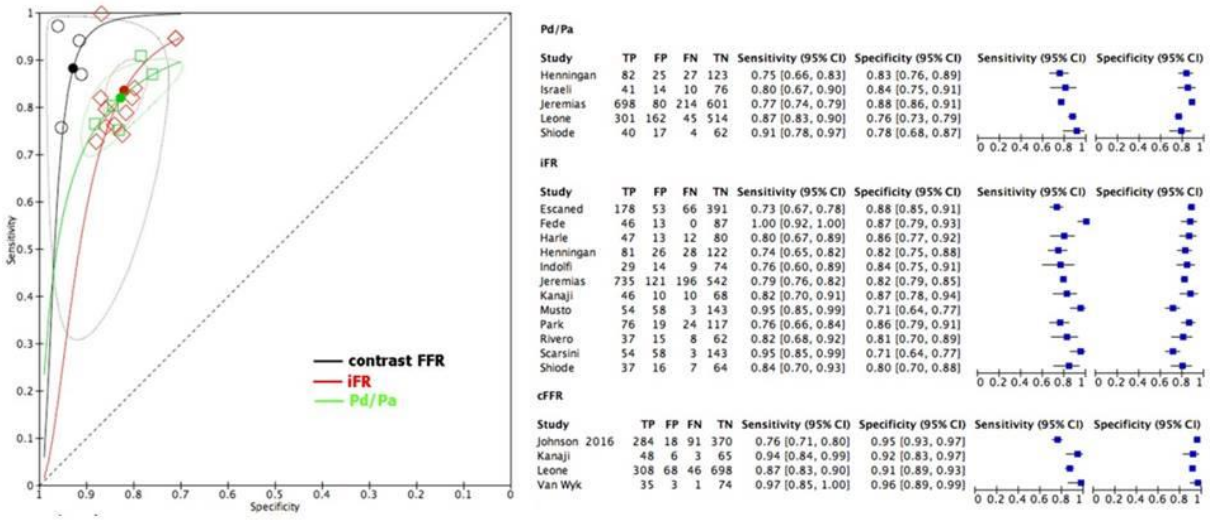
CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 2.

3.7 Functional evaluation systems

3.7.1 Rationale for the equivalence of different functional assessments

In the present study, we include different systems for the evaluation of coronary physiology. In particular, we considered as equivalent FFR and adenosine free-indices such as instantaneous wave-free ratio (iFR), contrast FFR (cFFR), and angiography-derived-FFR. This equivalence has been demonstrated by two important recent meta-analyses. Leone et al (34) analyzed the correlation between adenosine-free indexes (AFI) and fractional flow reserve (FFR) and to compare their diagnostic accuracy when FFR is used as reference. Authors included 18 studies with 4424, 4822 and 2021 coronary lesions in 4410, 4472 and 1898 patients were evaluated by Pd/Pa, iFR and cFFR, respectively. The overall Pearson's correlations were 0.81 (95%CI 0.78-0.83), 0.80 (95%CI 0.78-0.81) and 0.92 (95%CI 0.90-0.94) for Pd/Pa, iFR and cFFR, respectively. cFFR showed a significantly higher correlation with FFR compared to Pd/Pa and iFR (p<0.0001). The area under the HSROC estimating the discriminating accuracy of cFFR was 0.95 (95%CI 0.94-0.96) and it was

significantly higher compared to Pd/Pa (0.86, 95%CI 0.80-0.93) and iFR (0.89, 95%CI 0.84-0.94) (p<0.0001) (34).



Another important meta-analysis by Collet et al (35) determined the diagnostic performance of angiography-derived FFR for the diagnosis of hemodynamically significant coronary artery disease. Thirteen studies comprising 1842 vessels were included. A Bayesian bivariate meta-analysis yielded a pooled sensitivity of 89% (95% credible interval 83-94%), specificity of 90% (95% credible interval 88-92%), positive likelihood ratio (+LR) of 9.3 (95% credible interval 7.3-11.7) and negative likelihood ratio (-LR) of 0.13 (95% credible interval 0.07-0.2). The summary area under the receiver-operating curve was 0.84 (95% credible interval 0.66-0.94). Meta-regression analysis did not find differences between the methods for pressure-drop calculation (computational fluid dynamics vs. mathematical formula), type of analysis (on-line vs. off-line) or software packages.

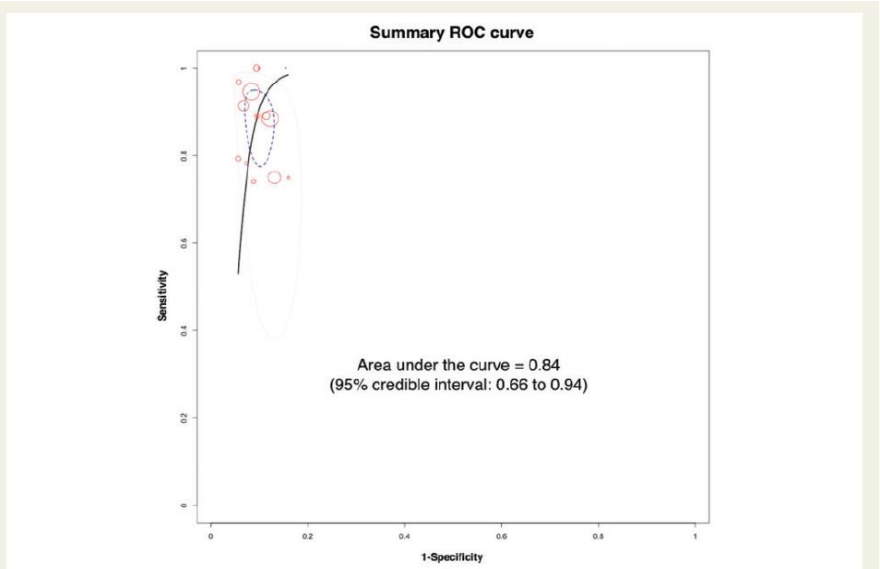


Figure 4 Summary of receiver operating curve. Each bubble represents one study and indicates its observed sensitivity and specificity. The size of the bubble is proportional to the number of individuals in this study. The solid black line is the summary of receiver operating curve line. The star point represents the summary point, the dashed blue line is the 95% credible region, and the dashed grey line is the 95% prediction region. The area under the summary receiver operating curve was 0.84 (95% credible interval 0.66–0.94).

In addition, current European Revascularization Guidelines acknowledged the same level of evidence to guide revascularization to FFR and iwFR (17).

Risk models to assess short- and long-term outcomes after myocardial revascularization	Class[a]	Level[b]
When evidence of ischaemia is not available, FFR or iwFR are recommended to assess the haemodynamic relevance of intermediate-grade stenosis.	I	A

3.7.2 Fractional flow reserve (FFR)

FFR, defined as the ratio of maximum flow in the presence of a stenosis to normal maximum flow, is a lesion-specific index of stenosis severity that can be calculated by simultaneous measurement of mean arterial, distal coronary, and central venous pressure (Pa, Pd, and Pv, respectively), during pharmacological vasodilation. FFR is measured with a coronary pressure guidewire at maximum hyperaemia induced by intravenous adenosine. It is allowed the use of intracoronary adenosine to induce hypermedia at discretion of the operator. FFR is defined as the ratio between the mean distal coronary pressure and the mean aortic pressure, during steady-state maximum hyperaemia. FFR value is considered potentially flow limiting, and therefore positive, if ≤0.80.

3.7.3 Instantaneous wave-free ratio (iwFR)

The instantaneous wave-free ratio (iwFR) is used to assess the severity of coronary-artery stenosis. Trans-stenotic pressure gradients at rest are predominantly determined by compensatory vasodilator changes in microvascular resistance. Therefore, according to the homeostatic principles of coronary autoregulation, for a stenosis to have a meaningful physiological impact upon the flow of blood to the myocardium, it should have a gradient that is detectible at rest. iwFR measures pressure during the wave free period (WFP) of diastole. The defining features of the WFP of diastole are: 1) flow velocity is approximately 30% higher than whole-cycle resting flow velocity; 2) intracoronary pressure and flow decline together in a linear fashion; and 3) microvascular resistance is significantly more stable and lower than that over the rest of the cardiac cycle. By means of the distal pressure value obtained during the WFP of diastole, iFR measures the physiological impact of a coronary stenosis on the distal coronary bed. The index has been tested against FFR in small trials, and the two measures have been found to have similar diagnostic accuracy. Recently, the DEFINE-FLAIR and IFR-SWEDEHEART trials demonstrated iFR non inferiority in comparison with FFR on clinical outcomes (36,37). The internationally recognized threshold for positive iFR is ≤0.89. Several companies have developed resting indices (Diastolic Pressure Ratio [dPR], Resting Full-cycle Ratio [RFR]) that are superimposable to the iFR from Philips that has been the first developed and tested in randomized trials.

3.7.4 Contrast FFR (cFFR)

Inducing hyperemia carries some cost and risk. A potential strategy to avoid adenosine infusion is intracoronary injection of contrast medium in order to induce some degree of hyperemia. This observation dates back to 1959 in animals (38) and first used in 1974 for assessing human physiological stenosis severity (39). Because of its ubiquity in the catheterization laboratory, contrast medium could provide an easy and inexpensive tool for assessing FFR, so-called contrast FFR (cFFR). The actual cutoff for positive cFFR is ≤0.85.

3.7.5 Quantitative Flow Ratio (QFR)

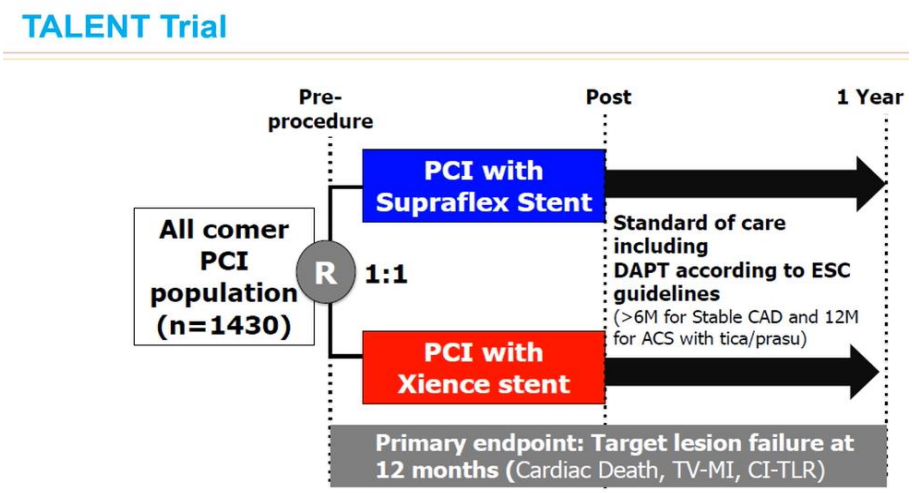
Quantitative flow ratio (QFR) is an emerging tool able to evaluate stenosis functional significance through a 3D flow reconstruction of the vessel based on 2 perpendicular angiograms. The main advantage of this technology is the avoidance of pressure wire and adenosine and the possibility to perform online evaluation. Recently, the Functional Diagnostic Accuracy of Quantitative Flow Ratio in Online Assessment of Coronary Stenosis (FAVOR) II China study showed a good online feasibility of QFR (40), while preliminary retrospective analysis from the Evaluation of the Xience-V Stent in Acute Myocardial Infarction (EXAMINATION) trial showed that QFR computation may be a safe and reliable tool to guide coronary revascularization of non-culprit lesions in ST-segment–elevation myocardial infarction patients (41). Thus, it could be an interesting opportunity to guide revascularization also in elderly patients with NSTEACS. The actual QFR cutoff is ≤0.80.

3.8 Elderly patients and revascularization with stent

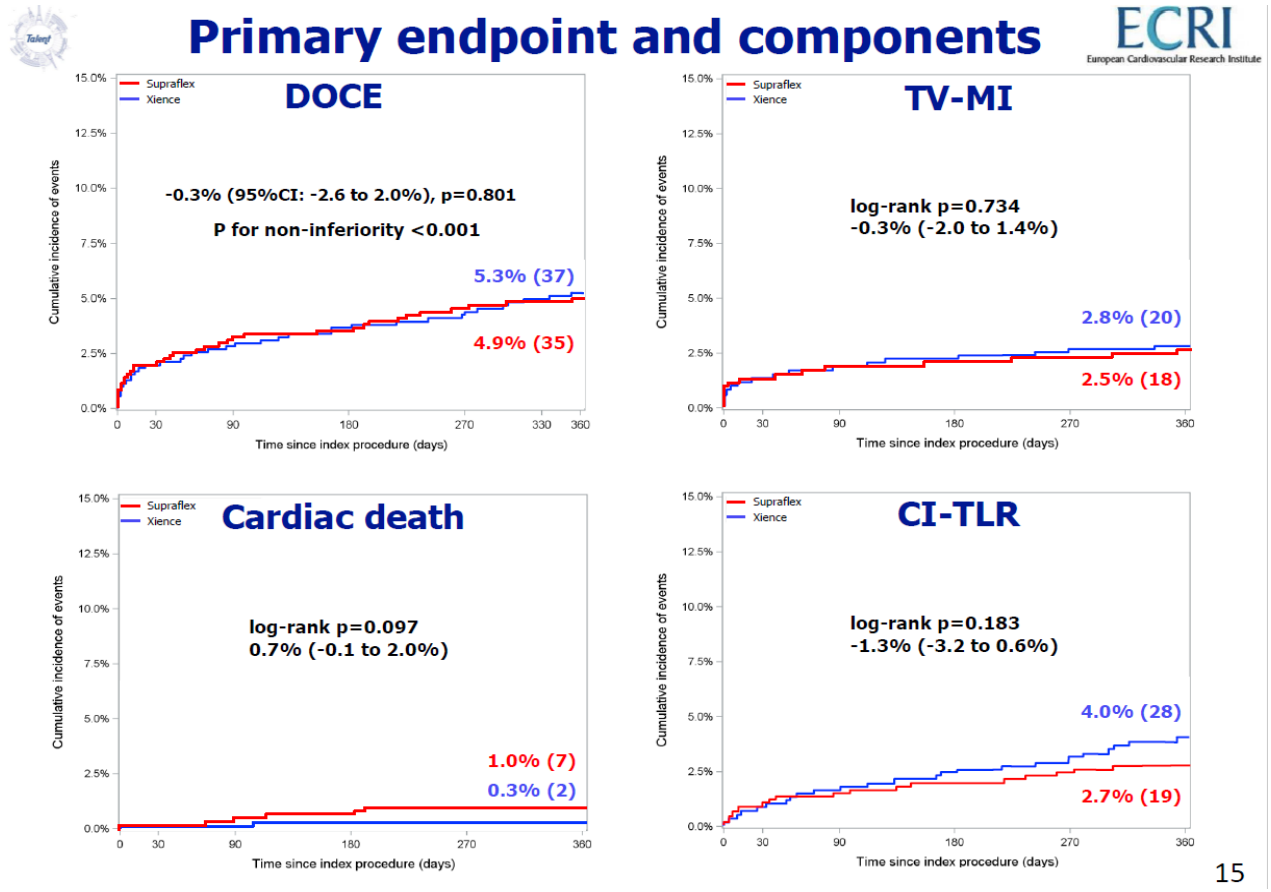
Elderly patients are usually excluded from the clinical trials aimed at the validation of new devices such as stents. Thus, there are actually few data regarding which stent is preferable in this subset of patients. The only randomized trial to date in this population is the Drug-eluting stents in elderly patients with coronary artery disease (SENIOR) trial (12). Patients ≥75 years with clinical indication to stent implantation were randomized to a biodegradable polymer DES or to a bare metal stent (BMS) with a short dual antiplatelet therapy (DAPT) regimen in both arms. 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 TLR. Thus, the preferred device in elderly patients is biodegradable polymer DES. Recently, a new stent received CE-approval. Supraflex (Sahajanand Medical Technologies Pvt Ltd, Surat, India) is a biodegradable polymer-coated sirolimus-eluting stent (SES).

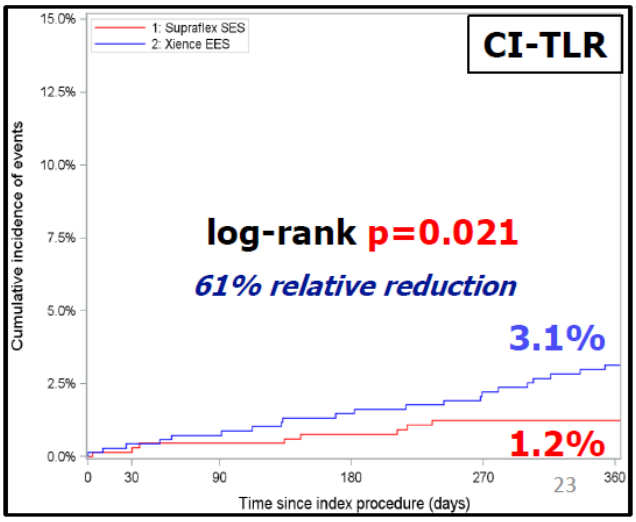
The most relevant novelty of this platform is represented by the ultrathin (60 µm) cobalt–chromium (Co–Cr) struts stent. Moreover, it will probably allow an even shorter duration of DAPT since its struts are the

thinnest actually available. For the same reason, in another ongoing contemporary trial focusing on elderly 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). Supraflex has been utilized in more than 12.000 patients worldwide. The results of Supraflex registries are in line with those of the other second generation DES (42). Recently, the results of the "Thin Strut Sirolimus-eluting Stent in All Comers Population vs Everolimus-eluting Stent (TALENT)" all-comers trial" have been presented (NCT02870140).



Supraflex was non-inferior to the actual best in class (Xience, Abbott) in terms of device oriented 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). In addition, a novel version of the device will be soon released (Supraflex Cruz). It remains unknown if these peculiar characteristics will translate in a better outcome, especially in elderly patients.

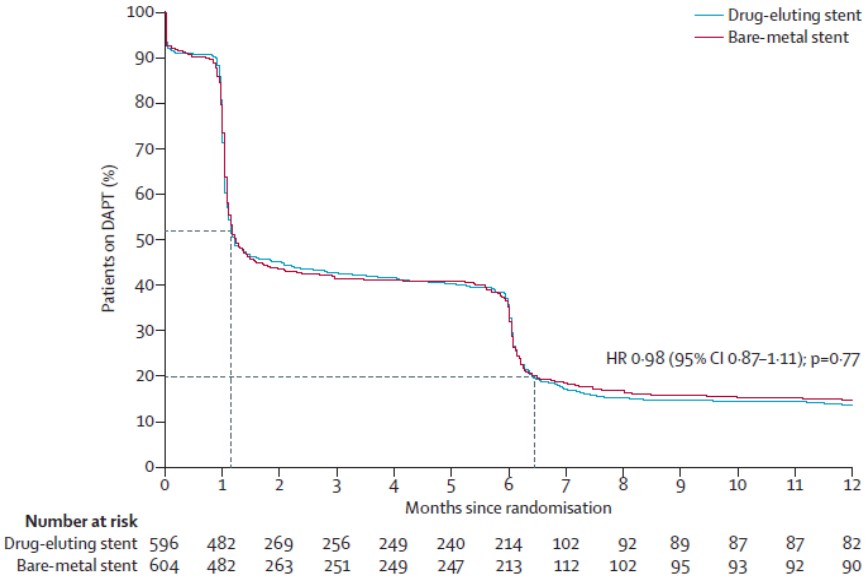




3.9 Dual antiplatelet therapy in elderly patients

In the SENIOR trial (12), elderly patients undergoing PCI were treated with a short DAPT regimen ranging from 1 to 6 months. Roughly 50% of patients DAPT was interrupted at 1 month with a good clinical outcome in the overall population. In addition, age ≥ 75 years is one of the criteria for high-bleeding risk in all bleeding risk scores such as PARIS Bleeding score and PRECISE-DAPT score. Thus, elderly patients with MI

and multivessel disease are both at high- ischemic and bleeding risk and the balance between these two competing risks is particularly complex. Due to this reason and to the results of the SENIOR trial, a stent with biodegradable polymer is the standard of care in this subset of patients. In fact, a relevant portion of patients will have to limit DAPT duration as much as possible due to clinical events or high-bleeding risk.



4 RATIONALE

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) (43).

5 STUDY 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 elderly patients with MI and multivessel PCI

5.2 Main 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 device oriented composite endpoint (DOCE) of cardiovascular (CV) death, MI or non-culprit target vessel revascularization (TVR) 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 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 the composite endpoint of 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

5.3 Exploratory endpoints

- 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

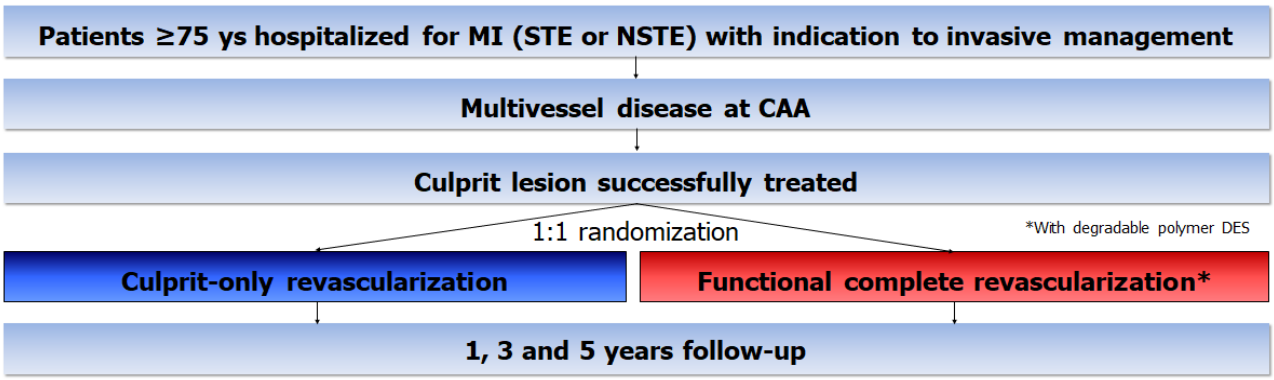
- To test if non-invasive functional strategy based on QFR evaluation is superior to a culprit only strategy in terms of target lesion failure (TLF) at 1, 3 and 5 years
- To test if functional strategy based on AFI evaluation is superior to a culprit only strategy in terms of target lesion failure (TLF) 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 test if functional strategy based on AFI evaluation is superior to a culprit only strategy in terms of ischemia-driven revascularization at 1, 3 and 5 years
- To test if non-invasive functional evaluation (QFR) is non-inferior to an invasive functional strategy (FFR, iwFR, cFFR) in terms of target lesion failure (TLF) at 1, 3 and 5 years
- To test if functional evaluation with AFI is non-inferior to an invasive functional strategy (FFR, iFR, cFFR) in terms of target lesion failure (TLF) at 1, 3 and 5 years
- To test if non-invasive functional evaluation (QFR) is non-inferior to an invasive functional strategy (FFR, iwFR, cFFR) in terms of ischemia driven revascularization at 1, 3 and 5 years
- To test if functional evaluation AFI is non-inferior to an FFR guided strategy in terms of ischemia driven revascularization at 1, 3 and 5 years
- 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

6 STUDY DESIGN, SCREENING AND RANDOMIZATION

6.1 Study design

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

6.2 Study flow chart



6.3 Screening

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.

6.4 Randomization

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 randomization list stratified by center. Randomization will also be stratified by sex and clinical presentation (STE vs NSTE-MI). All patients who are randomized are irrevocably in the study, whether or not they are subsequently found to be eligible, or actually receiving the allocated treatment. Therefore, all patients must be followed until the pre-specified study end date.

7 STUDY POPULATION

7.1 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

7.2 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
6. Left Main lesion as non-culprit

8 STUDY PROCEDURES

8.1 Management Strategies

After CAA and before randomization, Operator must indicate the culprit lesion and all diseased vessels (based on % stenosis at visual estimation). This information must be reported in eCRF before randomization.

8.1.1 General information regarding revascularization

Drug eluting stents with biodegradable polymer with struts ≤65 μ should be implanted. If feasible, each patient should receive revascularization with a single stent brand. Considering the outcome data and the technical characteristics, it is highly suggested to utilize Supraflex stent or its newer versions. 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. Presence of Chronic Total Occlusion (CTO) is not an exclusion criterion per se, although, it is needed another non culprit lesion ≥50% to randomize the patient.

8.1.2 Culprit-only Revascularization Strategy

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.

8.1.3 Complete Revascularization Functionally-guided

Patients who are randomized to this strategy will receive revascularization of the culprit lesion and guided by functional assessment on all non-culprit lesions. Functional evaluation is mandatory for all stenosis with diameter stenosis % between 50 and 90% at visual estimation, while it is suggested but not mandatory for all stenosis between 91 and 99%. Revascularization must be guided by functional assessment on all vessels. 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. Drug eluting stents with biodegradable polymer with struts ≤65 µ must be implanted in all non-culprit lesions with positive functional assessment. Routine stress testing and repeat angiography are not indicated in patients whose symptoms are stable. CTO management in the complete revascularization group is left to the Operators' discretion according to the clinical practice of his/her Institution. It is suggested to achieve functional complete revascularization within the index procedure, while it is mandatory to obtain it within the index hospitalization.

8.1.4 Optimal Medical Therapy (OMT)

All patients regardless of randomization group will receive OMT. Unless there is an absolute contraindication, all patients will receive standard secondary prevention with:

1. Aspirin 75-100 mg po daily
2. Ticagrelor 180 mg loading dose then 90 mg po BID unless contraindicated. DAPT duration is as for Institutional protocols, considering that age ≥75 is itself a criterion for high bleeding risk and that guidelines suggest at most 6 months of DAPT in this subset of patients. However, in very high bleeding risk: in patients, namely those with one of the following criteria:

- Clinical indication for chronic (at least 6 months) or lifelong anticoagulation therapy.
- History of major bleeding which required medical attention within 12 months of the index procedure.
- History of stroke (ischemic or hemorrhagic).
- Renal insufficiency (creatinine ≥ 2.0 mg/dl) or failure (dialysis dependent).
- Systemic conditions associated with an increased bleeding risk (e.g. hematological disorders, including a history of or current thrombocytopenia defined as a platelet count <100,000/mm3, or any known coagulation disorder associated with increased bleeding risk).
- Anemia with hemoglobin < 11g/dl.
- PRECISE-DAPT score>24.

Antiplatelet agent choice is left to the Physicians' discretion and it is mandatory to reduce DAPT duration to 1 month.

3. An ACE inhibitor or ARB appropriately titrated to target a blood pressure of < 130/85. If the patient continues to experience hypertension with BP > 130/85, additional blood pressure lowering treatments should be added: either a thiazide diuretic or dihydropyridine calcium channel blocker. The goal of antihypertensive therapy is to achieve and maintain a target blood pressure (BP) of < 130/85 mm Hg.
4. Statin therapy: Atorvastatin 40-80 mg daily or rosuvastatin 20-40 mg daily or simvastatin 40 mg daily. If, at any time during follow-up, the LDL cholesterol is above the target of 70 mg/dl, the statin dose should be further maximized (if not already attempted). If this still does not result in the desired effect, then ezetimibe can be added. If a patient has a statin related side effect, then, either a lower dose of the same statin or use of a different statin with or without the addition of ezetimibe can be considered.
5. If the patient is diabetic, the goal is to maintain fasting blood glucose levels between 80-135 mg/dl and hemoglobin A1c levels <7.0%, in accordance with published recommendations of International Guidelines. If these criteria are not met on oral hypoglycemic therapy, then insulin should be strongly considered.
6. If the patient has significant LV dysfunction, consideration should be given to administration of an aldosterone antagonist.

8.1.5 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).

Optimal medical antianginal therapy is considered as per guidelines and suggested by a recent consensus document (44). Nitrates, β-blockers, calcium-channel blockers, Ivabradine and Ranolazine must be all attempted and titrated to the maximum tolerated dose.

Table 1 | **Drugs for angina: pharmacology, symptom relief, outcomes benefits, and guideline recommendations**

Antianginal drug	HR	SBP	DBP	PVR	CC	CV	Symptom relief	Outcomes benefit	ESC*	ACC/AHA*
Nitrates										
Short-acting	↑–	↓↓	↓↓	↓–	–	↑↑↑	Yes	No	IB	IB
Long-acting	↑–	↓	↓	↓–	–	↑↑	Yes	No	IIB	IB
β-Blockers										
Noncardioselective	↓↓↓	↓↓	↓↓	↑–	↓↓	–	Yes	No	IA	IB
Cardioselective (preserved EF)	↓↓↓	↓↓	↓↓	–	↓↓	–	Yes	No	IA	IB
Cardioselective (reduced EF)	↓↓↓	↓↓	↓↓	–	↓↓	–	Yes	Yes	IB	IB
With vasodilatation (preserved EF)	↓↓	↓↓↓	↓↓↓	↓↓	↓	–	Yes	No	IB	IB
With vasodilatation (reduced EF)	↓↓	↓↓↓	↓↓↓	↓↓	↓	–	Yes	Yes	IA	IA
Calcium-channel blockers										
Dihydropyridines	↑–	↓↓↓	↓↓↓	↓↓↓	↑–	↑↑↑	Yes	No	IA	IB
Nondihydropyridines	↓↓	↓↓	↓↓	↓↓	↓↓	↑↑	Yes	No	IA	IIB
Other (considered second-choice treatment in guidelines)										
Ivabradine	↓↓	↓–	↓–	–	–	–	Yes	No	II_aB	NA
Nicorandil	↑	↓↓	↓↓	↓–	–	↑↑↑	Yes	Yes	II_aB	NA
Ranolazine	–	–	–	–	–	–	Yes	No	II_aB	IIA
Trimetazidine	–	–	–	–	–	–	Yes	No	II_bB	NA

*Guideline classification of benefit: class I – benefit >>> risk; class II_a – benefit >> risk; class II_b – benefit > risk. Level of evidence: A – one or two large, randomized trials; B – one randomized trial or small meta-analysis. CC, cardiac contractility; CV, coronary vasodilatation; DBP, diastolic blood pressure; EF, ejection fraction; HR, heart rate; NA, not available; PVR, peripheral vascular resistance; SBP, systolic blood pressure.

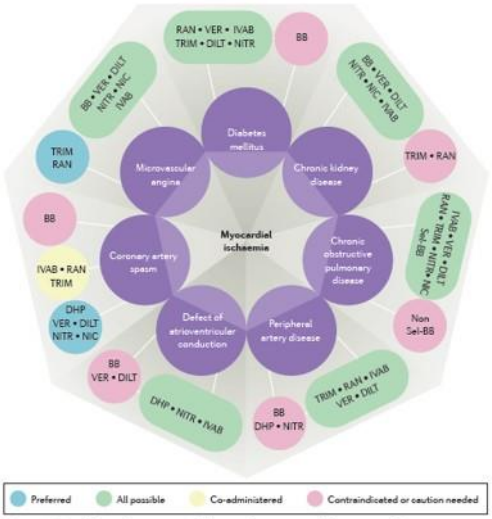


Figure 5 | **Possible combinations of classes of antianginal drugs according to different comorbidities.** BB, β-blockers; DHP, dihydropyridine calcium-channel blockers; DILT, diltiazem; IVAB, ivabradine; NIC, nicorandil; NITR, nitrates; Non Sel-BB, nonselective β-blockers; RAN, ranolazine; Sel-BB, β_1-selective blockers; TRIM, trimetazidine; VER, verapamil.

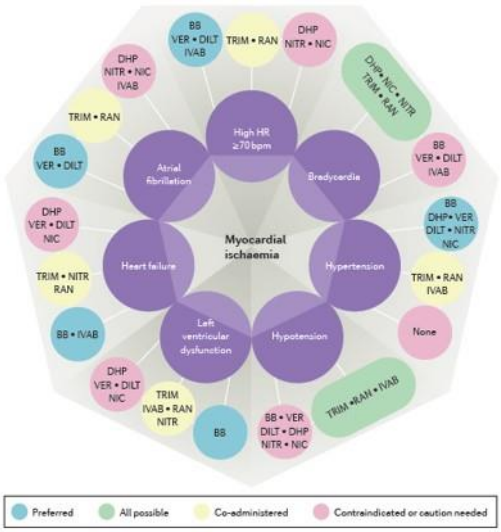


Figure 4 | **Possible combinations of classes of antianginal drugs according to different comorbidities.** BB, β-blockers; DHP, dihydropyridine calcium-channel blockers; DILT, diltiazem; HR, heart rate; IVAB, ivabradine; NIC, nicorandil; NITR, nitrates; RAN, ranolazine; TRIM, trimetazidine; VER, verapamil.

8.1.6 Index Coronary Angiogram and Functional Assessment

The initial angiogram and PCI for the index CAA and the functional assessment performed in the Functionally-driven arm should be recorded, anonymized and maintained locally for shipment to the angiographic and functional core lab (CD, DVD or digital files are acceptable).

8.1.7 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 3 years. At each visit, clinical outcomes (death, MI, stroke, bleeding), 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 at the 12-month and 3 year-follow-up visit.

9 STUDY DEFINITIONS

9.1 Myocardial Infarction (MI)

MI will be defined according to the 4th universal definition of myocardial infarction (45).

Universal definitions of myocardial injury and myocardial infarction

Criteria for myocardial injury

The term myocardial injury should be used when there is evidence of elevated cardiac troponin values (cTn) with at least one value above the 99th percentile upper reference limit (URL). The myocardial injury is considered acute if there is a rise and/or fall of cTn values.

Criteria for acute myocardial infarction (types 1, 2 and 3 MI)

The term acute myocardial infarction should be used when there is acute myocardial injury with clinical evidence of acute myocardial ischaemia and with detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL and at least one of the following:

- Symptoms of myocardial ischaemia;
- New ischaemic ECG changes;
- Development of pathological Q waves;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology;
- Identification of a coronary thrombus by angiography or autopsy (not for types 2 or 3 MIs).

Post-mortem demonstration of acute athero-thrombosis in the artery supplying the infarcted myocardium meets criteria for *type 1 MI*.
Evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute athero-thrombosis meets criteria for *type 2 MI*.
Cardiac death in patients with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes before cTn values become available or abnormal meets criteria for *type 3 MI*.

Criteria for coronary procedure-related myocardial infarction (types 4 and 5 MI)

Percutaneous coronary intervention (PCI) related MI is termed *type 4a MI*.
Coronary artery bypass grafting (CABG) related MI is termed *type 5 MI*.
Coronary procedure-related MI ≤ 48 hours after the index procedure is arbitrarily defined by an elevation of cTn values > 5 times for *type 4a MI* and > 10 times for *type 5 MI* of the 99th percentile URL in patients with normal baseline values. Patients with elevated pre-procedural cTn values, in whom the pre-procedural cTn level are stable (≤ 20% variation) or falling, must meet the criteria for a > 5 or > 10 fold increase and manifest a change from the baseline value of > 20%. In addition with at least one of the following:

- New ischaemic ECG changes (this criterion is related to *type 4a MI* only);
- Development of new pathological Q waves;
- Imaging evidence of loss of viable myocardium that is presumed to be new and in a pattern consistent with an ischaemic aetiology;
- Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or graft, side-branch occlusion-thrombus, disruption of collateral flow or distal embolization.

Isolated development of new pathological Q waves meets the *type 4a MI* or *type 5 MI* criteria with either revascularization procedure if cTn values are elevated and rising but less than the pre-specified thresholds for PCI and CABG.
Other types of 4 MI include *type 4b MI* stent thrombosis and *type 4c MI* restenosis that both meet *type 1 MI* criteria.
Post-mortem demonstration of a procedure-related thrombus meets the *type 4a MI* criteria or *type 4b MI* criteria if associated with a stent.

Criteria for prior or silent/unrecognized myocardial infarction

Any one of the following criteria meets the diagnosis for prior or silent/unrecognized MI:

- Abnormal Q waves with or without symptoms in the absence of non-ischaemic causes.
- Imaging evidence of loss of viable myocardium in a pattern consistent with ischaemic aetiology.
- Patho-anatomical findings of a prior MI.

The leading symptom that initiates the diagnostic and therapeutic cascade in patients with suspected MI is chest pain. Based on the electrocardiogram (ECG), two groups of patients should be differentiated: (1) Patients with acute chest pain and persistent (>20 min) ST-segment elevation. This condition is termed ST-elevation ACS and generally reflects an acute total coronary occlusion. Most patients will ultimately

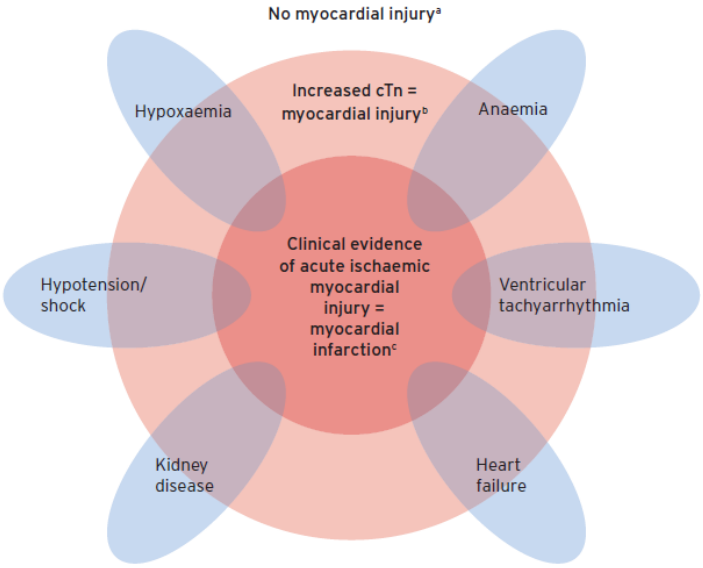
develop an ST-elevation myocardial infarction (STEMI). The mainstay of treatment in these patients is immediate reperfusion by primary angioplasty or fibrinolytic therapy. (2) Patients with acute chest pain but no persistent ST-segment elevation. ECG changes may include transient ST-segment elevation, persistent or transient ST-segment depression, T-wave inversion, flat T waves or pseudo-normalization of T waves or the ECG may be normal. The clinical spectrum of NSTE-MI may range from patients free of symptoms at presentation to individuals with ongoing ischemia, electrical or hemodynamic instability or cardiac arrest. The pathological correlate at the myocardial level is cardiomyocyte necrosis. A small proportion of patients may present with ongoing myocardial ischemia, characterized by one or more of the following: recurrent or ongoing chest pain, marked ST depression on 12-lead ECG, heart failure and hemodynamic or electrical instability. Due to the amount of myocardium in jeopardy and the risk of malignant ventricular arrhythmias, immediate coronary angiography and, if appropriate, revascularization are indicated.

9.1.1 Clinical criteria for MI

The clinical definition of MI denotes the presence of acute myocardial injury detected by abnormal cardiac biomarkers in the setting of evidence of acute myocardial ischaemia.

9.1.2 Criteria for myocardial injury

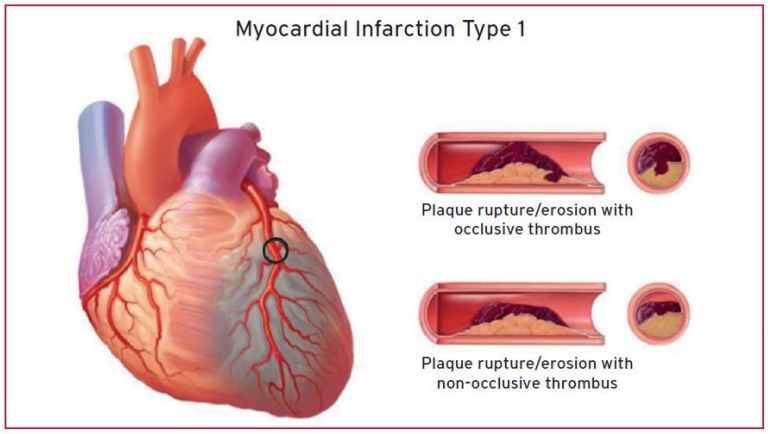
Detection of an elevated cTn value above the 99th percentile URL is defined as myocardial injury. The injury is considered acute if there is a rise and/or fall of cTn values.



Criteria for type 1 MI

Detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL and with at least one of the following:

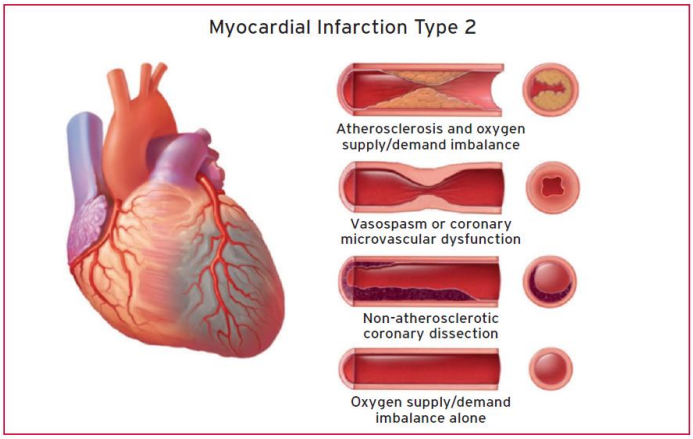
- Symptoms of acute myocardial ischaemia;
- New ischaemic ECG changes;
- Development of pathological Q waves;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology;
- Identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy.[a]



Criteria for type 2 MI

Detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL, and evidence of an imbalance between myocardial oxygen supply and demand unrelated to coronary thrombosis, requiring at least one of the following:

- Symptoms of acute myocardial ischaemia;
- New ischaemic ECG changes;
- Development of pathological Q waves;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology.



Criteria for type 3 MI

Patients who suffer cardiac death, with symptoms suggestive of myocardial ischaemia accompanied by presumed new ischaemic ECG changes or ventricular fibrillation, but die before blood samples for biomarkers can be obtained, or before increases in cardiac biomarkers can be identified, or MI is detected by autopsy examination.

9.2 Death

Deaths will be classified as cardiovascular, non-cardiovascular or undetermined cause according to ARC-2 criteria (43). Deaths of undetermined cause will default to cardiovascular (but will also be reported as a separate subcategory of cardiovascular death to denote this uncertainty). Deaths related to the procedure or complications of the procedure (or concomitant treatment) will be classified as cardiovascular. Within cardiovascular deaths, hemorrhagic deaths will be clearly identified. Only deaths due to a documented non-cardiovascular cause (e.g., cancer) will be classified as non-cardiovascular.

ARC-2 classification of death:

Type of Death	Definition
Cardiovascular death	Cardiovascular death is defined as death resulting from cardiovascular causes. The following categories may be collected: 1. Death caused by acute MI 2. Death caused by sudden cardiac, including unwitnessed, death 3. Death resulting from heart failure 4. Death caused by stroke 5. Death caused by cardiovascular procedures 6. Death resulting from cardiovascular hemorrhage 7. Death resulting from other cardiovascular cause
Noncardiovascular death	Noncardiovascular death is defined as any death that is not thought to be the result of a cardiovascular cause. The following categories may be collected: 1. Death resulting from malignancy 2. Death resulting from pulmonary causes 3. Death caused by infection (includes sepsis) 4. Death resulting from gastrointestinal causes 5. Death resulting from accident/trauma 6. Death caused by other noncardiovascular organ failure 7. Death resulting from other noncardiovascular cause
Undetermined	Undetermined cause of death is defined as a death not attributable to any other category because of the absence of any relevant source documents. Such deaths will be classified as cardiovascular for end point determination.

MI indicates myocardial infarction.

9.3 Ischemia-driven revascularization

Requires the following criteria:

1. Ischemic symptoms consistent with CCS class ≥ 3 angina despite optimal medical therapy

AND

2. PCI or CABG of either the culprit or a non-culprit lesion that lead to enrollment into the trial PLUS at least ONE of the following:

A. Positive functional study (Exercise or myocardial perfusion imaging or stress or dobutamine echo) demonstrating clear evidence of reversible ischemia corresponding to a stenosis in a vessel other than the culprit vessel that lead to enrollment into the trial,

OR

B. New ischemic ECG changes (ST-segment depression ≥ 1 mm, ST-segment elevation ≥ 1 mm or T wave inversion ≥ 2 mm) at rest or with exertion in a distribution consistent with a stenosis in a vessel other than the culprit vessel that lead to enrollment into the trial,

OR

C. FFR ≤0.80, iFR≤0.89, cFFR≤0.85, QFR≤0.80 in a lesion in a vessel other than the culprit vessel that lead to enrollment into the trial.

All ischemic-driven revascularizations will be sub-categorized as to whether they were due to the culprit lesion or due to a non-culprit lesion that led to enrollment into the trial.

9.4 Stent Thrombosis

Stent thrombosis will be defined according to ARC-2 criteria (35). Definition and timing of stent thrombosis (43):

Classification	Criteria
Definite stent/scaffold thrombosis	Angiographic confirmation of stent/scaffold thrombosis* The presence of a thrombus† that originates in the stent/scaffold or in the segment 5 mm proximal or distal to the stent/scaffold or in a side branch originating from the stented/scaffolded segment and the presence of at least 1 of the following criteria: Acute onset of ischemic symptoms at rest New electrocardiographic changes suggestive of acute ischemia Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous myocardial infarction) Or Pathological confirmation of stent/scaffold thrombosis Evidence of recent thrombus within the stent/scaffold determined at autopsy Examination of tissue retrieved following thrombectomy (visual/histology)
Probable stent/scaffold thrombosis	Regardless of the time after the index procedure, any myocardial infarction that is related to documented acute ischemia in the territory of the implanted stent/scaffold without angiographic confirmation of stent/scaffold thrombosis and in the absence of any other obvious cause.‡
Silent stent/scaffold occlusion	The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered stent thrombosis.
Timing of ST (duration after stent implantation)	
Acute	0§–24 h
Subacute	>24 h–30 d
Late	>30 d–1 y
Very late	>1 y

Early stent thrombosis is 0 to 30 days (acute plus subacute stent thrombosis). MI indicates myocardial infarction.
*Definite stent/scaffold thrombosis is considered to have occurred by either angiographic or pathological confirmation.
†Occlusive thrombus: Thrombolysis in Myocardial Infarction grade 0 or 1 flow within or proximal to a stent/scaffold segment. Nonocclusive thrombus: intracoronary thrombus is defined as a (spherical, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, persistence of contrast material within the lumen, or visible embolization of intraluminal material downstream.
‡When the stented/scaffolded segment is in the left circumflex coronary artery or in the presence of preexisting electrocardiographic abnormalities (eg, left bundle branch block, paced rhythms), definitive evidence of localization may be absent and Clinical Events Committee adjudication is based on review of all available evidence).
§Defined as the moment the patient is undraped and taken off the catheterization table.

9.5 Stroke

Defined as the presence of a new focal neurologic deficit thought to be vascular in origin, with signs or symptoms lasting more than 24 hours. It is strongly recommended (but not required) that an imaging procedure such as CT scan or MRI be performed. Stroke will be further classified as ischemic, hemorrhagic or type uncertain.

9.6 Nonfatal Cardiac Arrest

Successful resuscitation from either documented or presumed ventricular fibrillation or ventricular tachycardia or asystole.

9.7 Contrast-induced Acute Kidney Injury (AKI)

Contrast-induced AKI is defined as any of the following:

- Increase in Serum Creatinine (SCr) by X0.3 mg/dl (X26.5 lmol/l) within 48 hours; or
- Increase in SCr to X1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or

- Urine volume o0.5 ml/kg/h for 6 hours

Staging of AKI is showed in the following Table.

Table 2 | Staging of AKI

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline OR ⩾0.3 mg/dl (⩾26.5 µmol/l) increase	<0.5 ml/kg/h for 6–12 hours
2	2.0–2.9 times baseline	<0.5 ml/kg/h for ⩾12 hours
3	3.0 times baseline OR Increase in serum creatinine to ⩾4.0 mg/dl (⩾353.6 µmol/l) OR Initiation of renal replacement therapy OR, In patients <18 years, decrease in eGFR to <35 ml/min per 1.73 m^2	<0.3 ml/kg/h for ⩾24 hours OR Anuria for ⩾12 hours

9.8 Quality of life, Physical performance and Economic assessments

The Seattle Angina Questionnaire and the EQ-5D questionnaire will be used to measure quality of life. Short physical performance battery (SPPB) will be used for physical performance evaluation. In addition, costs will be collected during the course of the study, including medical and resource utilization (including medication and cardiac procedures), re-hospitalizations and emergency room visits.

9.9 Adjudication of clinical events

A committee consisting of clinicians who are blinded to treatment allocation will adjudicate primary and secondary efficacy outcomes (death, MI, stroke, revascularization). 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.

10 STATISTICAL ANALYSIS PLAN

All statistical analyses will be performed by the Centro di Ricerca Clinica ed Epidemiologica of the University of Ferrara under the supervision of Professor Stefano Volpato. Analysis will be performed on an Intention to Treat (ITT) set, defined as all intentionally randomized patients, by randomization treatment. Supportive per-protocol analyses will be performed on the primary and key secondary endpoints. A detailed statistical analysis plan will be completed before the end of the study. In brief, continuous variables will be tested for normal distribution with the Kolmogorov-Smirnov test and with visual estimate of Q-Q plot. Normally distributed variables will be presented as mean±SD and compared by t test and 1-way ANOVA. Otherwise, median [inter-quartile range], Mann-Whitney U and Kruskal-Wallis tests will be used. Categorical variables will be summarized in terms of absolute and relative frequencies (percentages) and compared by using $\chi 2$ test. One-sided tests will be done in order to check the superiority of functionally-driven complete revascularization. Statistical significance will be set at $\alpha=0.05$ level. Formal type-I error control will be ensured for the primary and the key secondary endpoint by a sequential procedure where significance for the key secondary endpoint is accepted only if the primary endpoint is positive. Kaplan-Meyer curves will be plot to describe survival free from adverse events, and difference between groups will be test will log-rank test. The primary analysis will be based on events of all follow-up time of each patient at the time of the database lock. Further analyses will be performed with events after more than 30 days considered as censored, as well as after more than 365 days considered as censored. Any confounding factor will be tested by Cox regression models. Variables with a p-value <0.1 at univariate analysis will be entered into a multivariable analysis to identify the independent predictors. When appropriate, 95% CI will be calculated. In addition, we will assess the composite primary outcome POCE (all-cause mortality, any MI, any stroke and any revascularization) 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. This method gives a higher importance to all-cause mortality. The pairwise comparison proceeds in 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 We will apply the Finkelstein–

Schoenfeld method to the patients stratified according to clinical presentation (STE vs NSTE) and number of diseased vessels (2 vs 3), yielding four stratification pools. All analyses will be performed with STATA 13 (StataCorp, College Station, TX).

10.1 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) 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 1385 patients. 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.

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 revascularisation	0.56 [0.38-0.83]

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

11 SUB-STUDIES

Sub-studies may be added at a later date based on the recommendation of the Steering Committee. The analysis and reporting of these sub-studies will be totally separate from the main study.

12 DATA MANAGEMENT

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' must be done by the investigator and is considered to be the final authorization of the CRFs.

13 ANGIOGRAPHIC AND FUNCTIONAL CORE LAB

The central core lab will review all the angiographies from the enrolling centers and will review the evaluation of the culprit lesion and the % diameter stenosis and the functional evaluation of all the stenosis with evaluation of the functional pitfalls. If centers will not properly evaluate culprit lesion or if relevant pitfalls in the functional evaluation will be present in more than 3 cases in the same center, the center will receive a proper retraining on functional evaluation. If the center even after the functional retraining will not be able to perform a proper functional evaluation, the enrollment will be stopped.

14 ETHICAL AND REGULATORY STANDARDS

14.1 Good Clinical Practice

The procedures set out in this protocol are designed to ensure that the investigator abide by the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines (ICH-GCP) in the latest version, in conduct, evaluation and documentation of the study. A copy of these documents will be provided to each centre. The study will be carried out in keeping with local legal requirements and International regulations.

14.2 Informed Consent of the Patient

Patients who meet all inclusion criteria and none of the exclusion criteria are deemed eligible. Before being enrolled into the clinical study, the patient must provide written consent to participate in the study after the nature, scope and possible consequences of the clinical study have been explained both orally and in writing. Patients should be aware that they will be followed for the study whether or not they undergo invasive strategy as allocated. All patients who signed informed consent must be listed on the Screening Log.

14.3 Approval of the Study Protocol

Before the start of the study, the study protocol and the informed consent form used at the site and other appropriate documents must be submitted to and approved by the local Ethics Committee or Institutional Review Board and the appropriate regulatory authorities in accordance with local legal requirements. Documentation of Ethics Committee/IRB approvals will be required before sites are activated to randomize.

14.4 Maintenance of Records

The Investigator agrees to obtain a correctly completed informed consent form for each patient included in the study. The investigator will maintain a personal list of patient numbers and patient names to enable records to be found at a later date. The Investigator must maintain all study records, patient files and other source data for the maximum period of time permitted by the hospital, institution or private practice. However national regulations should be taken into account, the longest time having to be considered. For

trials performed in the European Community, the Investigator is required to arrange for the retention of the patient identification codes for at least 15 years after the completion or discontinuation of the trial.

14.5 Confidentiality

All patient names will be kept confidential. Patients will be identified throughout documentation and evaluation by the number allotted to them by the study. The patients will be assured that all findings will be stored on computer and handled in the strictest confidence. The Investigator agrees to maintain the confidentiality of the study protocol.

15 ADMINISTRATIVE RULES

15.1 Curriculum vitae

An updated copy of the curriculum vitae for each Investigator and co-Investigator will be provided prior to the beginning of the study.

15.2 Confidentiality agreement

All goods, materials, information (oral or written) and unpublished documentation provided to the Investigators (or any company acting on their behalf), inclusive of this protocol and the patient case report forms are the exclusive property of the Cardiovascular Department of the University of Ferrara. They may not be given or disclosed by the Investigator or by any person within his authority either in part or in totality to any unauthorized person without the prior written formal consent. It is specified that the submission of this protocol and other necessary documentation to the ERC or a like body (IRB, CCPPRB...) is expressly permitted, the Ethics Committee members having the same obligation of confidentiality. The Investigator shall consider as confidential and shall take all necessary measures to ensure that there is no breach of confidentiality in respect of all information accumulated, acquired or deduced in the course of the trial, other than that information to be disclosed by law.

15.3 Record retention in investigating centre(s)

The Investigator must maintain all study records, patient files and other source data for the maximum period of time permitted by the hospital, institution or private practice. National regulations, however, should be taken into account, the longest time having to be considered. For trials performed in the European Community, the Investigator is required to arrange for the retention of the patient identification codes for at least 15 years after the completion or discontinuation of the trial.

16 OWNERSHIP OF DATA AND USE OF THE STUDY RESULTS

The Study Principal Investigator and the Study Chair have ownership of all data and results collected during this study. Full publication rights of the study data solely reside with the Study Principal Investigator and the Study Chair.

17 PUBLICATIONS

All study presentations and/or publication of the results will be based on clean, checked and validated data in order to ensure the accuracy of the results. Publication of the main findings of this study will be authored based on the contributions of the individuals to the overall study. All the trial participants (Investigators and committee members) make a prior delegation of responsibility for primary presentation and/or primary publication of the results to the Study Principal Investigator and the Study Chair.

18 STUDY ADMINISTRATIVE INFORMATION

18.1 Address list

18.1.1 Sponsor

Professor Laura Ramaciotti

Via Saragat, 1 - Block B – 1st floor - 44122 Ferrara, Italy

Telephone number: +39 0532 974082

18.1.2 Principal Investigator

Doctor Simone Biscaglia

Via Aldo Moro 8, Block 1D2, 44123 Cona (Ferrara), Italy

Telephone number: +39 0532 239883

18.1.3 Study Chair

Professor Gianluca Campo

Via Aldo Moro 8, Block 1D2, 44123 Cona (Ferrara), Italy

Telephone number: +39 0532 236450

18.2 INSURANCE

Subjects who participate in this study will be insured against study related injury according to local regulatory requirements. A copy of the certificate is filed in each investigator site file and in the trial master file.

18.3 FUNDING AND SUPPORT

This study is an Investigator Initiated Trial supported by an unrestricted grant from different public and private companies (for details see attachment – appendix A). Study supporters have no role in the study design, conduct, and publication of the primary as well as any secondary manuscripts.

19 REFERENCES

1. Madhavan MV, Gersh BJ, Alexander KP, Granger CB, Stone GW. Coronary Artery Disease in Patients ≥80 Years of Age. J Am Coll Cardiol. 2018;71:2015-2040.
2. Gnanenthiran SR, Kritharides L, D'Souza M, Lowe HC, Brieger DB. Revascularisation compared with initial medical therapy for non-ST-elevation acute coronary syndromes in the elderly: a meta-analysis. Heart. 2017;103:1962-1969.
3. Wald DS, Morris JK, Wald NJ, et al.; PRAMI Investigators. Randomized trial of preventive angioplasty in myocardial infarction. N Engl J Med 2013;369:1115-23.
4. Gershlick AH, Khan JN, Kelly DJ, et al. Randomized trial of complete versus lesion-only revascularization in patients undergoing primary percutaneous coronary intervention for STEMI and multivessel disease: the CvLPRIT trial. J Am Coll Cardiol 2015;65:963-72.
5. Hlinomaz O. Multivessel coronary disease diagnosed at the time of primary PCI for STEMI: complete revascularization versus conservative strategy: the PRAGUE 13 trial. Presented at: EuroPCR; May 19, 2015; Paris, France. http://sbhci.org.br/wp-content/uploads/2015/05/PRAGUE-13-Trial.pdf [accessed October 19, 2017].
6. Engstrøm T, Kelbæk H, Helqvist S, et al.; DANAMI-3–PRIMULTI Investigators. Complete revascularization versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3–PRIMULTI): an open-label, randomised controlled trial. Lancet 2015;386:665-71.
7. Smits PC, Abdel-Wahab M, Neumann FJ, et al.; Compare-Acute Investigators. Fractional flow reserve-guided multivessel angioplasty in myocardial infarction. N Engl J Med 2017;376:1234-44
8. Lee PY, Alexander KP, Hammill BG, Pasquali SK, Peterson ED. Representation of elderly persons and women in published randomized trials of acute coronary syndromes. JAMA 2001;286: 708–13
9. Mariani J, Macchia A, De Abreu M, Gonzalez Villa Monte G, Tajer C. Multivessel versus single vessel angioplasty in non-ST elevation acute coronary syndromes: a systematic review and metaanalysis. PloS One 2016;11:e0148756.
10. Rathod KS, Koganti S, Jain AK, Astroulakis Z, Lim P, Rakhit R, Kalra SS, Dalby MC, O'Mahony C, Malik IS, Knight CJ, Mathur A, Redwood S, Sirker A, MacCarthy PA, Smith EJ, Wragg A, Jones DA. Complete Versus Culprit-Only Lesion Intervention in Patients With Acute Coronary Syndromes. J Am Coll Cardiol. 2018;72:1989-1999.
11. Hambraeus K, Jensevik K, Lagerqvist B, et al. Long-term outcome of incomplete revascularization after percutaneous coronary intervention in SCAAR (Swedish Coronary Angiography and Angioplasty Registry). J Am Coll Cardiol Intv 2016;9: 207–15.
12. Sardella G, Lucisano L, Garbo R, et al. Single-Staged Compared With Multi-Staged PCI in Multivessel NSTEMI Patients: The SMILE Trial. J Am Coll Cardiol. 2016;67:264-72.
13. Layland J, Oldroyd KG, Curzen N, et al. Fractional flow reserve vs. angiography in guiding management to optimize outcomes in non-ST-segment elevation myocardial infarction: the British Heart Foundation FAMOUS-NSTEMI randomized trial. Eur Heart J. 2015;36:100-11.
14. Nam J, Briggs A, Layland J, et al. Fractional flow reserve (FFR) versus angiography in guiding management to optimise outcomes in non-ST segment elevation myocardial infarction (FAMOUS-NSTEMI) developmental trial: cost-effectiveness using a mixed trial- and model-based methods. Cost Eff Resour Alloc. 2015;13:19.
15. Varenne O, Cook S, Sideris G, et al. Drug-eluting stents in elderly patients with coronary artery disease (SENIOR): a randomised single-blind trial. Lancet. 2018;391:41-50.
16. Lee SY, Hong MK, Palmerini T, et al. Short-Term Versus Long-Term Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation in Elderly Patients: A Meta-Analysis of Individual Participant Data From 6 Randomized Trials. JACC Cardiovasc Interv. 2018;11:435-443.
17. Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2016;37:267-315.
18. Salinas GLA, Fernández MS, Izco MP, et al. Frailty is a short-term prognostic marker in acute coronary syndrome of elderly patients. Eur Heart J Acute Cardiovasc Care 2016: 5: 434–440.

19. Yazji K, Abdul F, Elangovan S, et al. Comparison of the Effects of Incomplete Revascularization on 12-Month Mortality in Patients <80 Compared With ≥80 Years Who Underwent Percutaneous Coronary Intervention. Am J Cardiol. 2016;118:1164-1170.
20. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, Jüni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferovic PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO; ESC Scientific Document Group . 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2018 Aug 25. doi: 10.1093/eurheartj/ehy394.
21. Bebb O, Smith FG, Clegg A, Hall M, Gale CP. Frailty and acute coronary syndrome: A structured literature review. Eur Heart J Acute Cardiovasc Care. 2017:2048872617700873.
22. Feldman L, Steg PG, Amsallem M, Puymirat E, Sorbets E, Elbaz M, Ritz B, Hueber A, Cattan S, Piot C, Ferrières J, Simon T, Danchin N. Medically managed patients with non-ST-elevation acute myocardial infarction have heterogeneous outcomes, based on performance of angiography and extent of coronary artery disease. Eur Heart J Acute Cardiovasc Care. 2017;6:262-271.
23. Wang TY, McCoy LA, Bhatt DL, Rao SV, Roe MT, Resnic FS, Cavender MA, Messenger JC, Peterson ED. Multivessel vs culprit-only percutaneous coronary intervention among patients 65 years or older with acute myocardial infarction. Am Heart J. 2016;172:9-18.
24. Garot P, Morice MC, Tresukosol D, Pocock SJ, Meredith IT, Abizaid A, Carrié D, Naber C, Iñiguez A, Talwar S, Menown IBA, Christiansen EH, Gregson J, Copt S, Hovasse T, Lurz P, Maillard L, Krackhardt F, Ong P, Byrne J, Redwood S, Windhövel U, Greene S, Stoll HP, Urban P; LEADERS FREE Investigators. 2-Year Outcomes of High Bleeding Risk Patients After Polymer-Free Drug-Coated Stents. J Am Coll Cardiol. 2017;69:162-171.
25. Panaich SS, Arora S, Patel N, et al. Comparison of In-Hospital Mortality, Length of Stay, Postprocedural Complications, and Cost of Single-Vessel Versus Multivessel Percutaneous Coronary Intervention in Hemodynamically Stable Patients With ST-Segment Elevation Myocardial Infarction (from Nationwide Inpatient Sample [2006 to 2012]). Am J Cardiol. 2016;118:950-8.
26. Zeitouni M, Silvain J, Guedeney P, et al. Periprocedural myocardial infarction and injury in elective coronary stenting. Eur Heart J. 2018;39:1100-1109.
27. Giacoppo D, Madhavan MV, Baber U, et al. Impact of Contrast-Induced Acute Kidney Injury After Percutaneous Coronary Intervention on Short- and Long-Term Outcomes: Pooled Analysis From the HORIZONS-AMI and ACUITY Trials. Circ Cardiovasc Interv. 2015;8:e002475.
28. McCullough PA, Choi JP, Feghali GA, Schussler JM, Stoler RM, Vallabahn RC, Mehta A. Contrast-Induced Acute Kidney Injury. J Am Coll Cardiol. 2016;68:1465-1473.
29. Xaplanteris P, Fournier S, Pijls NHJ, et al. Five-Year Outcomes with PCI Guided by Fractional Flow Reserve. N Engl J Med. 2018 May 22. doi: 10.1056/NEJMoa1803538. [Epub ahead of print].
30. Zimmermann F. A pooled patient-level analysis of FAME 2 DANAMI PRIMULTI and COMPARE-ACUTE trials. Oral presentation at EUROPCR 2018.
31. Hakeem A, Edupuganti MM, Almomani A, et al. Long-term prognosis of deferred acute coronary syndrome lesions based on nonischemic fractional flow reserve. J Am Coll Cardiol 2016;68: 1181–91.
32. Palmerini T, Della Riva D, Biondi-Zoccai G, et al. Mortality Following Nonemergent, Uncomplicated Target Lesion Revascularization After Percutaneous Coronary Intervention: An Individual Patient Data Pooled Analysis of 21 Randomized Trials and 32,524 Patients. JACC Cardiovasc Interv. 2018;11:892-902.
33. Kobayashi Y, Lønborg J, Jong A, Nishi T, De Bruyne B, Høfsten DE, Kelbæk H, Layland J, Nam CW, Pijls NHJ, Tonino PAL, Warnøe J, Oldroyd KG, Berry C, Engstrøm T, Fearon WF; Prognostic Value of the Residual SYNTAX Score After Functionally Complete Revascularization in ACS. J Am Coll Cardiol. 2018 Sep 18;72(12):1321-1329.
34. Leone AM, Campo G, Gallo F, Pavasini R, Basile E, D'Amario D, Tebaldi M, Biscaglia S, Maietti E, Trani C, Crea F. Adenosine-Free Indexes vs. Fractional Flow Reserve for Functional Assessment of Coronary Stenoses: Systematic Review and Meta-Analysis. In press.
35. Collet C, Onuma Y, Sonck J, Asano T, Vandeloo B, Kornowski R, Tu S, Westra J, Holm NR, Xu B, de Winter RJ, Tijssen JG, Miyazaki Y, Katagiri Y, Tenekecioglu E, Modolo R, Chichareon P, Cosyns B, Schoors D, Roosens B, Lochy S, Argacha JF, van Rosendael A, Bax J, Reiber JHC, Escaned J, De Bruyne B, Wijns W, Serruys PW. Diagnostic performance of angiography-derived fractional flow reserve: a systematic review and Bayesian meta-analysis. Eur Heart J. 2018;39:3314-3321.

36. Götberg M, Christiansen EH, Gudmundsdottir IJ, et al. Instantaneous Wave-free Ratio versus Fractional Flow Reserve to Guide PCI.N Engl J Med. 2017;376:1813-1823.
37. Davies JE, Sen S, Dehbi HM, et al Use of the Instantaneous Wave-free Ratio or Fractional Flow Reserve in PCI. N Engl J Med. 2017;376:1824-1834.
38. Guzman SV, West JW. Cardiac effects of intracoronary arterial injections of various roentgenographic contrast media. Am Heart J 1959;58:597–607.
39. Gould KL, Hamilton GW, Lipscomb K, Ritchie JL, Kennedy JW. Method for assessing stress-induced regional malperfusion during coronary arteriography. Experimental validation and clinical application. Am J Cardiol 1974;34:557–64.
40. Xu B, Tu S, Qiao S, et al. Diagnostic Accuracy of Angiography-Based Quantitative Flow Ratio Measurements for Online Assessment of Coronary Stenosis. J Am Coll Cardiol. 2017;70:3077-3087.
41. Spitaleri G, Tebaldi M, Biscaglia S, et al. 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.
42. Lemos PA, Chandwani P, Saxena S, et al. Clinical outcomes in 995 unselected real-world patients treated with an ultrathin biodegradable polymer-coated sirolimus-eluting stent: 12-month results from the FLEX Registry. BMJ Open. 2016 17;6:e010028.
43. Garcia-Garcia HM, McFadden EP, Farb A, Mehran R, Stone GW, Spertus J, Onuma Y, Morel MA, van Es GA, Zuckerman B, Fearon WF, Taggart D, Kappetein AP, Krucoff MW, Vranckx P, Windecker S, Cutlip D, Serruys PW; Academic Research Consortium. Standardized End Point Definitions for Coronary Intervention Trials: The Academic Research Consortium-2 Consensus Document. Eur Heart J. 2018 Jun 14;39(23):2192-2207.
44. Ferrari R, Camici PG, Crea F, Danchin N, Fox K, Maggioni AP, Manolis AJ, Marzilli M, Rosano GMC, Lopez-Sendon JL. Expert consensus document: A 'diamond' approach to personalized treatment of angina. Nat Rev Cardiol. 2018;15:120-132.
45. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD; ESC Scientific Document Group. Fourth universal definition of myocardial infarction (2018). Eur Heart J. 2018 Aug 25. doi: 10.1093/eurheartj/ehy462.