Functional Coronary **A**ngiography to **I**ndicate and Guide **R**evascularization in STEMI Patients with Multivessel Disease: the **AIR-STEMI** trial

Version number 1 of December 9th, 2022

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

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

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1 STUDY SYNOPSIS

Study Title:	Functional Coronary Angiography to Indicate and Guide Revascularization in STEMI Patients with Multivessel Disease: the AIR-STEMI trial
Protocol version:	V1
Date:	December 9th, 2022
Study Sponsor:	Azienda Ospedaliero Universitaria di Ferrara Azienda USL di Bologna Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy ***The present trial received the endorsement of the Italian Health Minister that partially supported the conduction of the study with the grant GR-2021-12372516 (Ricerca Finalizzata 2021)***
Study Principal Investigator:	Simone Biscaglia, MD
Study Objectives	The primary aim of the AIR-STEMI trial is to demonstrate the superiority in terms of efficacy of the Angiography-derived FFR strategy (AIR) over that based on conventional angiography (ANGIO). The primary endpoint of the study is the cumulative occurrence of all-cause death, myocardial infarction, cerebrovascular accident, or ischemia-driven revascularization. Secondary efficacy endpoints are the cumulative occurrence of: i) all-cause death, ii) CV death; iii) myocardial infarction, iv) ischemia driven coronary revascularization; iv) Quality Adjusted Life Years (QALYs). The primary safety endpoint of the study is the cumulative occurrence of contrast-associated acute kidney injury and bleeding BARC 3-5. Additional safety endpoint is the cumulative occurrence of periprocedural myocardial infarction. Finally, the last aim of the AIR-STEMI trial is to assess the cost-effectiveness of the Angiography-derived FFR strategy over conventional angiography.
Study design	AIR-STEMI is a comparative effectiveness study. Participants will be recruited following successful primary PCI and randomized in a 1:1 fashion to an AIR or ANGIO strategy.
Number of participants	1 800
Trial Location	Approximately 20 Italian sites

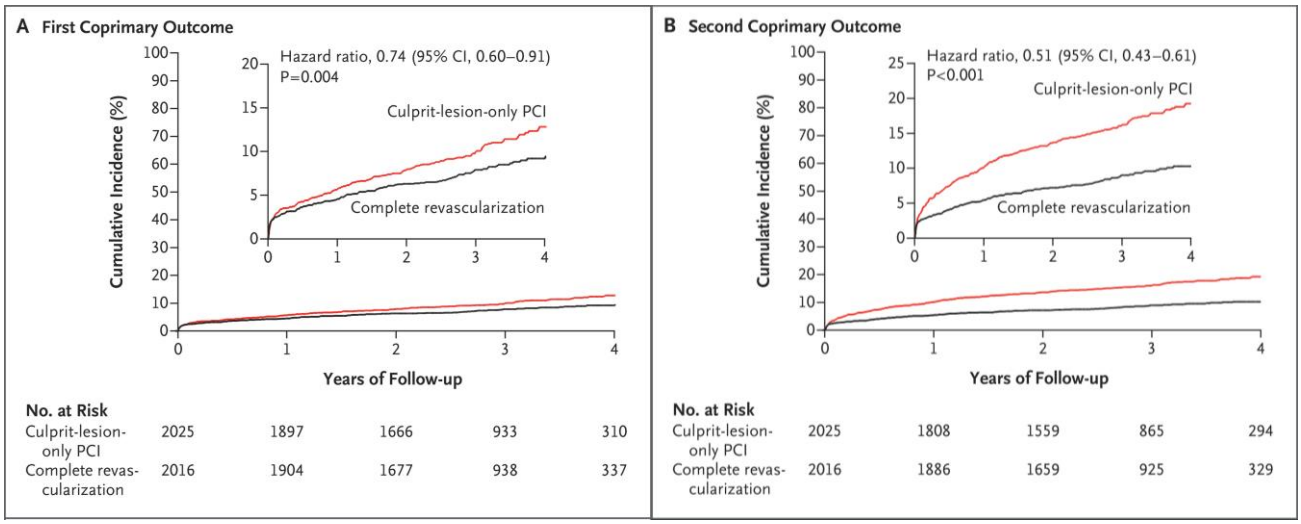
Inclusion criteria	1. STEMI with indication to invasive management (primary PCI) AND 2. Multi-vessel disease defined as at least one non-culprit coronary artery lesion at least 2.5 mm in diameter deemed at visual estimation with a diameter stenosis % ranging from 50 to 99% AND 3. Successful treatment of culprit lesion
Exclusion criteria	1. Planned surgical revascularization 2. Left main as non-culprit lesion 3. Non-cardiovascular co-morbidity reducing life expectancy to < 1 year 4. Any factor precluding 1-year follow-up 5. Prior Coronary Artery Bypass Graft (CABG) Surgery 6. Impossibility to identify a clear culprit lesion 7. Presence of a chronic total occlusion (CTO)
Primary endpoint	Efficacy: composite of all-cause death, cerebrovascular accident, myocardial infarction, or ischemia-driven revascularization. Safety: composite of contrast-associated acute kidney injury and bleeding BARC 3-5.
Secondary endpoints	• CV death • Non-fatal MI • Spontaneous MI • Periprocedural MI • Vessel oriented composite endpoint (VOCE) as defined as cardiovascular (CV) death, MI or non-culprit target vessel revascularization (TVR) • BARC 3-5 • Ischemic stroke • Stent thrombosis • Contrast-induced acute kidney injury • EQ-5D quality of life scale • EQ-5D VAS • Seattle Angina Questionnaire (SAQ) Frequency scale • Quality Adjusted Life Years (QALYs)
Assessment Schedule	Pre-eligibility screening, primary PCI, randomization, 1 months, 12 months, and every 12 months thereafter.
Study Duration	Enrolment will occur over approximately 2 years with an expected minimum of 12 months follow-up and an average of approximately 18-24 months follow-up.

Clinical Event Adjudication Committee	The following events will be adjudicated by a blinded Clinical Event Adjudication Committee: death, myocardial infarction, resuscitated cardiac arrest, hospitalization for unstable angina, hospitalization for heart failure, and stroke.
Data and Safety Monitoring Board	An independent Data and Safety Monitoring Board will advise the study leadership on safety aspects and overall progress of the study.
Statistical Considerations	To maximize the possibility to achieve important information, the follow-up will be censored for all patients when the last enrolled patient will achieve the 1-year follow-up. Considering that the recruitment will take around 20-22 months, we will have a median follow-up around 16-18 months, ranging from 12 to 22 months. The estimated occurrence of the primary endpoint according to previous studies is around 9% in the control group. In the FAVOR III China trial, the strategy based on angiography-derived FFR was able to reduce the composite primary efficacy endpoint by 35%. Therefore, 1718 patients are required to have an 80% chance of detecting, as significant at the 5% level, a 35% difference in the primary outcome between the two study groups considering a 9% rate of the primary endpoint in the control group. Considering a 5% attrition rate final sample size is inflated to 1800 patients.

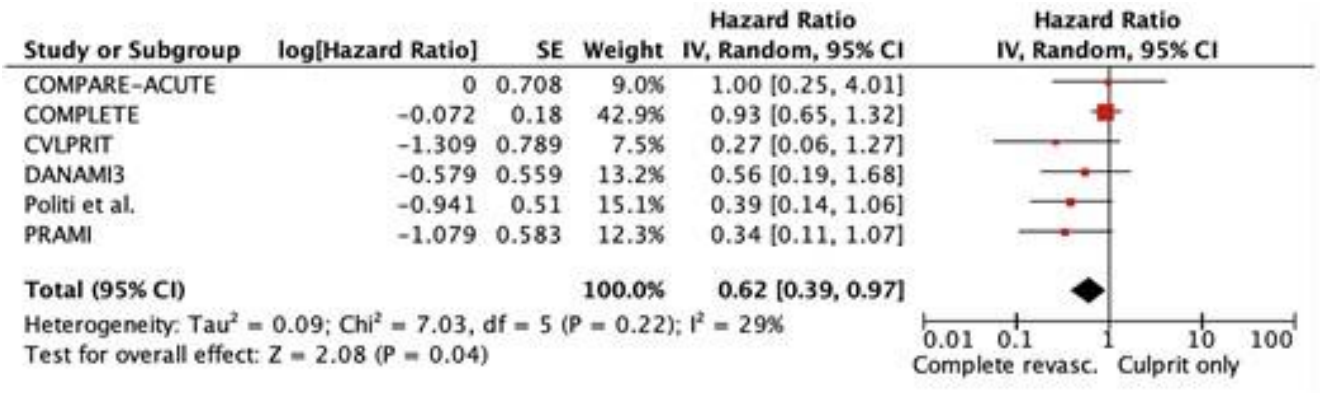
2 BACKGROUND

2.1 COMPLETE - Angio-guided complete revascularization reduces MI versus culprit only

Reperfusion of the culprit lesion through primary PCI is the standard of care in ST-segment elevation myocardial infarction (STEMI) patients, regardless of their age[1]. The management of non-culprit lesions in STEMI patients with multivessel disease (MVD) has been the focus of several randomized clinical trials (RCT) comparing culprit-only vs. complete revascularization strategies[2,3]. The Complete vs Culprit-only Revascularization to Treat Multi-vessel Disease after Primary PCI for STEMI (COMPLETE) trial randomized 4 041 patients with STEMI and MVD[2]. The main finding was the highly significant reduction of new MI occurrence in the complete group (7.9% vs 5.4%, HR 0.68, 95% CI 0.53-0.87, p=0.002). Revascularization was obtained largely by angiographic evaluation (>99%), since Investigators deemed only 0.6% lesions as intermediate (50-69%). Interestingly, when quantitative coronary angiography (QCA) was performed by the corelab, around 66% of lesions showed a % stenosis <70%. This confirms Investigators' reluctance to perform FFR.



A meta-analysis of the available studies comparing complete and culprit-only strategy showed a significant reduction of cardiovascular (CV) death. Overall, 6528 patients were included (3139 complete group, 3389 culprit-only group). After a follow-up ranging between 1 and 3 years (median 2 years), cardiovascular death was significantly reduced in the group receiving complete revascularization (HR 0.62, 95% CI 0.39-0.97, I2 = 29%). The number needed to treat to prevent one cardiovascular death was 70 (95% CI 36-150). The secondary endpoints MI and revascularization were also significantly reduced (HR 0.68, 95% CI 0.55-0.84, I2 = 0% and HR 0.29, 95% CI 0.22-0.38, I2 = 36%, respectively). Needed to treats were 45 (95% CI 37-55) for MI and 8 (95% CI 5-13) for revascularization. All-cause death (HR 0.81, 95% CI 0.56-1.16, I2 = 27%) was not affected by the revascularization strategy[3].



In conclusion, complete revascularization was superior to a culprit-only strategy thanks to a reduction of MI rate, which translated in a CV death reduction when all studies were pooled together.

2.2 FLOWER-MI - Angio- versus physio-guided complete revascularization: much ado about nothing?

After COMPLETE, the subsequent step was to ascertain which complete revascularization strategy should be pursued. In particular, physiology-guided revascularization was compared to an angio-guided strategy. The advantages of physiology against angiography are related to: a) lower number of vessels treated, b) lower number of stents implanted; c) avoidance of a second procedure in negative FFR patients during primary PCI; d) possibility to optimize the procedure from the physiological standpoint after percutaneous coronary intervention (PCI).

In the Flow Evaluation to Guide Revascularization in Multivessel ST-Elevation Myocardial Infarction (FLOWER-MI), patients with STEMI and multivessel disease who had undergone successful PCI of the infarct-related artery were randomly assigned to receive complete revascularization guided by either FFR or angiography. The primary outcome was a composite of death from any cause, nonfatal myocardial infarction, or unplanned hospitalization leading to urgent revascularization at 1 year. FFR-guided revascularization was associated with lower number of stents implanted per patient (1.01±0.99 versus 1.50±0.86). During follow-up, a primary outcome event occurred in 32 of 586 patients (5.5%) in the FFR-guided group and in 24 of 577 patients (4.2%) in the angiography-guided group (hazard ratio, 1.32; 95% confidence interval, 0.78 to 2.23; P = 0.31). Death occurred in 9 patients (1.5%) in the FFR-guided group and in 10 (1.7%) in the angiography-guided group; nonfatal myocardial infarction in 18 (3.1%) and 10 (1.7%), respectively; and unplanned hospitalization leading to urgent revascularization in 15 (2.6%) and 11 (1.9%), respectively.

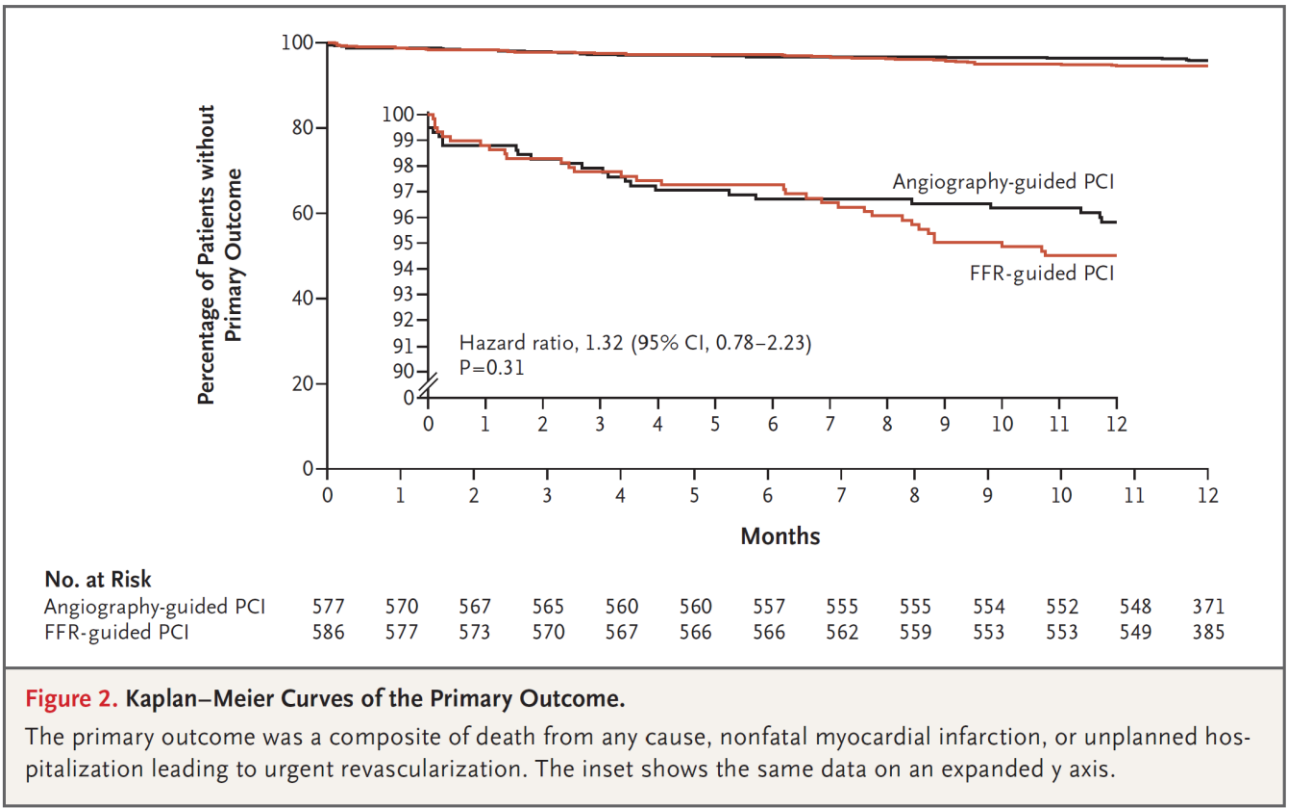


Figure 2. Kaplan–Meier Curves of the Primary Outcome.
The primary outcome was a composite of death from any cause, nonfatal myocardial infarction, or unplanned hospitalization leading to urgent revascularization. The inset shows the same data on an expanded y axis.

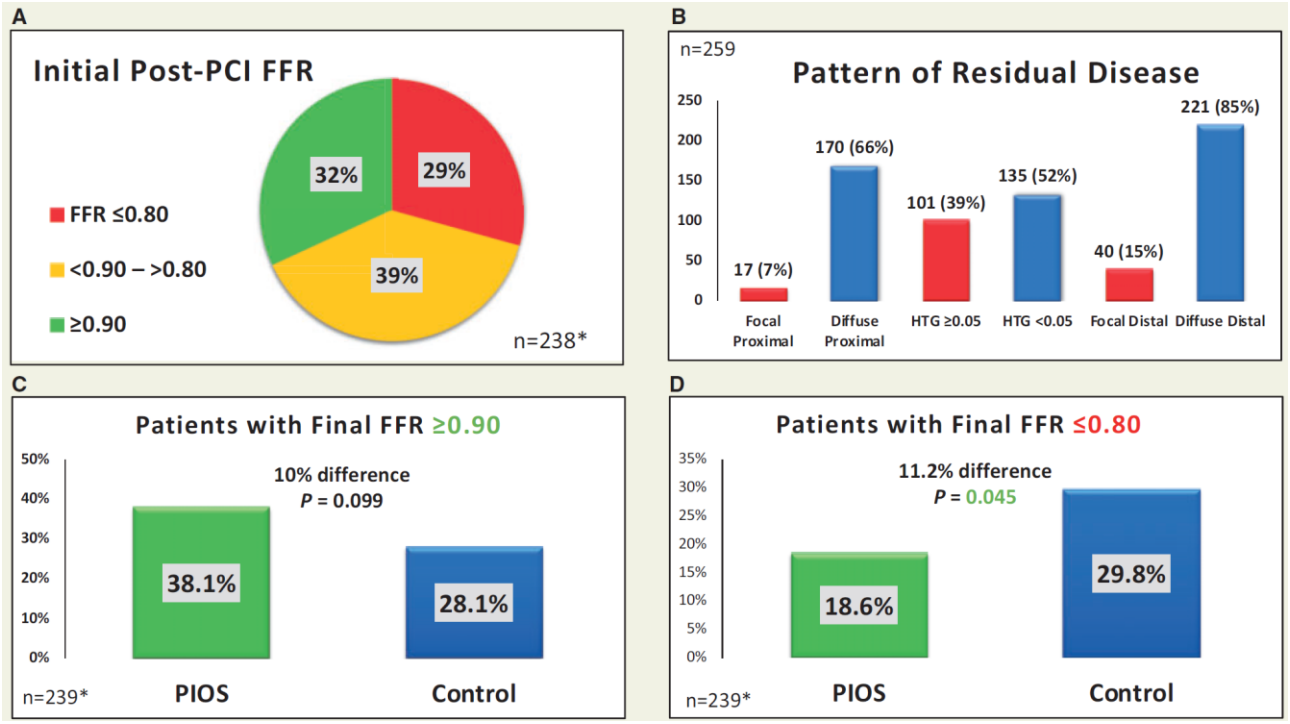
The results of the FLOWER-MI trial may suggest that physiology can provide a similar outcome if compared to a conventional angio-guided approach. However, some limitation should be acknowledged: i) rate of events was three-times lower than expected suggesting both a selection bias and the need of a higher number of patients to demonstrate any difference among the two groups; ii) all patients in the FFR-group received a staged procedure to perform physiology assessment diluting one of the major advantages in FFR negative patients, namely the avoidance of a second procedure if physiology is negative; iii) in 16% of patients in the physio-guided group FFR was not performed before PCI, whereas in 82% of patients it was not performed after PCI; iv) even if FFR was associated with lower PCIs, periprocedural MI was three times higher if compared to the angio-group, suggesting its possible underreporting in the angio-group.

2.3 TARGET FFR – the struggles of systematic PCI optimization with FFR

When FFR was utilized before, during and after PCI to improve physiological final result, results were two-faced. The Trial of Angiography vs. pressure-Ratio-Guided Enhancement Techniques—Fractional Flow Reserve (TARGET-FFR) was designed to assess the efficacy of a post-PCI physiology-guided incremental optimization strategy (PIOS) vs. standard angiographic guidance in achieving final post-PCI FFR values ≥0.90[4]. TARGET-FFR is an investigator-initiated, single-center, randomized controlled trial.

After angiographically guided PCI, patients were randomized 1:1 to receive a physiology-guided incremental optimization strategy (PIOS) or a blinded coronary physiology assessment (control group). The primary outcome was the proportion of patients with a final post-PCI FFR ≥0.90. Final FFR ≤0.80 was a prioritized secondary outcome. A total of 260 patients were randomized (131 to PIOS, 129 to control) and 68.1% of patients had an initial post-PCI FFR <0.90. In the PIOS group, 30.5% underwent further

intervention (stent post-dilation and/or additional stenting). There was no significant difference in the primary endpoint of the proportion of patients with final post-PCI FFR ≥0.90 between groups (PIOS minus control 10%, 95% confidence interval -1.84 to 21.91, P = 0.099). The proportion of patients with a final FFR ≤0.80 was significantly reduced when compared with the angiography-guided control group (-11.2%, 95% confidence interval -21.87 to -0.35], P = 0.045). It is noteworthy that only 38% of patients in the PIOS group obtained an FFR ≥0.90 whereas in 40% of the cases a corrective action followed an abnormal FFR.



TARGET-FFR results suggest that the ability to systematically obtain a good functional result is unlikely and not always possible.

2.4 Is Angiography-derived FFR any different?

Several Angiography-derived FFR are emerging as tools able to evaluate stenosis functional significance through a 3D flow reconstruction of the vessel based on 2 perpendicular angiograms. Several studies demonstrated the good correlation between wire-based and Angiography-derived FFR with a cut-off of 0.80.[5–11]

The main advantage of this technology is the avoidance of pressure wire and adenosine and the possibility to perform online evaluation. In a recent meta-analysis of 16 studies, 819 patients and 969 vessels with paired FFR and Angiography-derived FFR were included. Authors found an overall agreement (mean difference 0.009 ± 0.068, I2 = 39.6) of angiography- and wire- derived FFR. The diagnostic performance was sensitivity 84% (95%CI: 77-90, I2 = 70.1), specificity 88% (95%CI: 84-91, I2 = 60.1); positive predictive value 80% (95%CI: 76-85, I2 = 33.4), and negative predictive value 95% (95%CI: 93-96, I2 = 75.9)[10].

Several non-inferiority trials are ongoing to provide the definitive answer regarding Angiography-derived FFR clinical equivalence in comparison with wire-based FFR (NCT03729739, NCT04931771, NCT03497637, NCT04923191, NCT04575207).

Another interesting application of Angiography-derived FFR could be as a simple way to evaluate post PCI functional result. . The value of Angiography-derived FFR to assess the functional results of PCI has been tested in the prospective HAWKEYE (Angio-Based Fractional Flow Reserve to Predict Adverse Events After Stent Implantation) study. Seven hundred fifty-one vessels in 602 patients undergoing angiographically satisfactory second-generation DES implantation were analyzed [6]. At the end of the procedure, the operator acquired projections for Angiography-derived FFR computation performed offline by an independent core laboratory. ROC curve analysis identified a post-PCI Angiography-derived FFR best cut-off of ≤0.89 (area under the curve 0.77; 95% CI: 0.74-0.80; p< 0.001). After correction for potential confounding factors, post-PCI Angiography-derived FFR≤0.89 was associated with a 3-fold increase in risk for the vessel-oriented composite endpoint at 2 years (HR: 2.91; 95% CI 1.63-5.19; p< 0.001). In a retrospective evaluation of the SYNTAX II trial, the post-PCI Angiography-derived FFR threshold for prediction of VOCE at 2 years was similar, being <0.91 even in patients with anatomical complexity such as three-vessel disease[12].

Further, a very important finding of the HAWKEYE study was the demonstration that Angiography-derived FFR could discriminate among different CAD patterns. In vessels with suboptimal functional result, the site of the Angiography-derived FFR drop was in-stent in 13% of the cases, while a focal drop outside the stent was identifiable in 32% of the cases. Thirty-four percent of vessels showed diffuse disease, while in 21% a combination of the aforementioned possibilities was present.

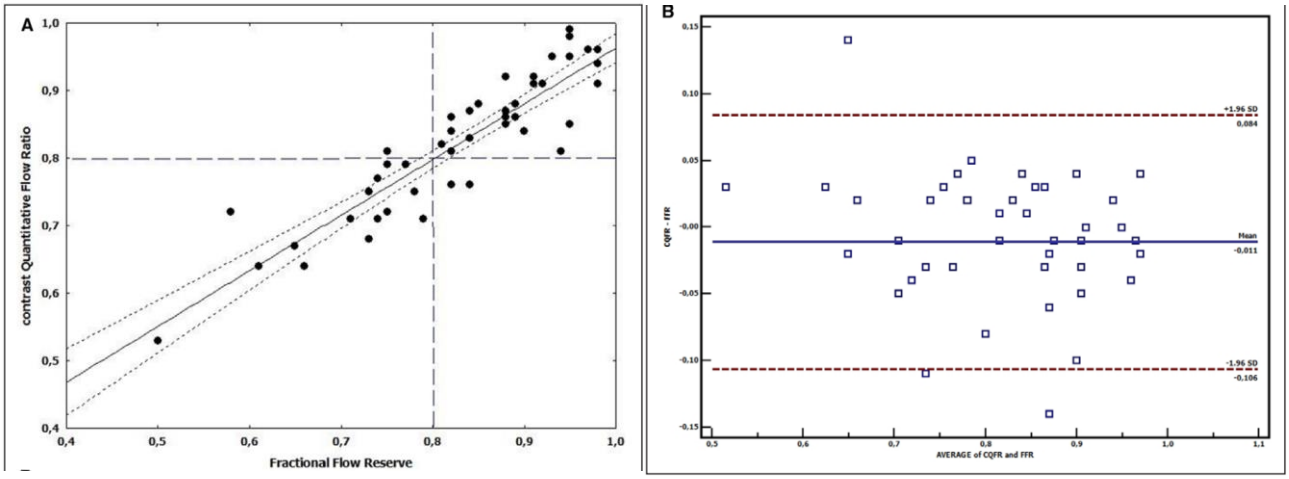
Angiography-derived FFR analyzability depends on quality of angiography and it is feasible in around 80% of the cases[6,12]. Moreover, Angiography-derived FFR is not applicable in specific lesion subsets such as left main, bifurcation and ostial lesions.

2.5 Angiography-derived FFR is feasible in STEMI setting

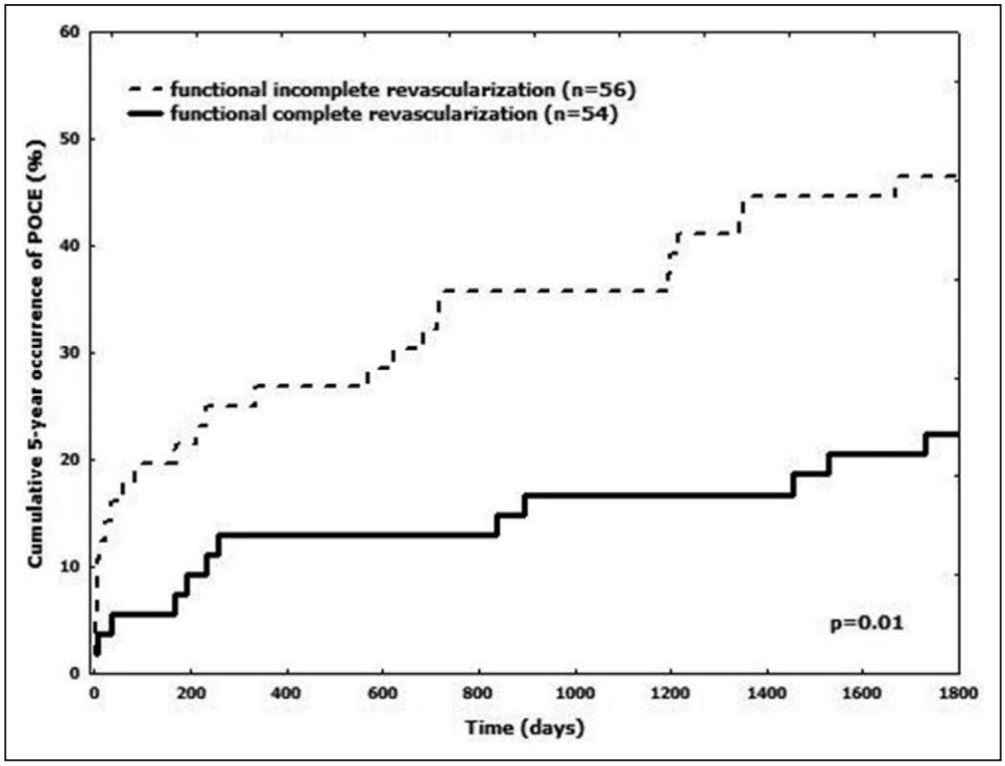
One of the theoretically most appealing setting for ANGIOGRAPHY-DERIVED FFR utilization is STEMI. Operator can acquire Angiography-derived FFR projections of the non-culprit lesion(s) during primary PCI and then perform off-line the analysis. Therefore, one of the major research field in the clinical validation of Angiography-derived FFR is STEMI.

A first proof-of-concept study identified Angiography-derived FFR reproducibility in non-culprit lesions (NCLs) assessment (cohort A, n=31); prospectively validated Angiography-derived FFR diagnostic accuracy in respect to FFR; and investigated long-term clinical outcomes of NCLs stratified according to Angiography-derived FFR. A blinded core laboratory computed Angiography-derived FFR values for all NCLs. Angiography-derived FFR values showed a good correlation and agreement both at index (acute) and at staged (subacute, 3-4 days later) procedures (r=0.98; 95% confidence interval, 0.96-0.99; mean difference, 0.004 [-0.027 to 0.34]). The inter-rater agreement was κ=0.9. FFR and Angiography-derived identified 16 (33%) and 17 (35%) NCLs potentially flow limiting. Sensitivity, specificity, negative, and positive predictive values were 88%, 97%, 94%, and 94%. The area under the receiver operating characteristics curve was 0.96

(95% confidence interval, 0.89-0.99). Finally, in 110 STEMI patients where at least 1 NCL was left untreated. Patients with NCLs showing a Angiography-derived FFR value ≤0.80 were at higher risk of adverse events (hazard ratio, 2.3; 95% confidence interval, 1.2-4.5; P=0.01)[8]. The present proof-of-concept study is based on a 3-step process: (1) identification of the Angiography-derived FFR reproducibility in NCLs assessment (cohort A, n=31); (2) prospective validation of Angiography-derived FFR diagnostic accuracy in respect to fractional flow reserve (cohort B, n=45); and (3) investigation of long-term clinical outcomes of NCLs stratified according to Angiography-derived FFR (cohort C, n=110). A blinded core laboratory computed Angiography-derived FFR values for all NCLs. Cohort A showed a good correlation and agreement between Angiography-derived FFR values at index (acute) and at staged (subacute, 3-4 days later) procedures (r=0.98; 95% confidence interval, 0.96-0.99; mean difference, 0.004 [-0.027 to 0.34]).



The inter-rater agreement was κ=0.9. In cohort B, fractional flow reserve and Angiography-derived FFR identified 16 (33%) and 17 (35%) NCLs potentially flow limiting. Sensitivity, specificity, negative, and positive predictive values were 88%, 97%, 94%, and 94%. The area under the receiver operating characteristics curve was 0.96 (95% confidence interval, 0.89-0.99). Finally, in cohort C, we identified 110 ST-segment-elevation myocardial infarction patients where at least 1 NCL was left untreated. Patients with NCLs showing a Angiography-derived FFR value ≤0.80 were at higher risk of adverse events (hazard ratio, 2.3; 95% confidence interval, 1.2-4.5; P=0.01).



Subsequent studies confirmed these preliminary findings. In a total of 792 patients with ACS (48.6% ST-segment-elevation ACS and 51.4% non-ST-segment-elevation ACS), Angiography-derived FFR analyses of postinterventional culprit (n=792 vessels) and non-culprit vessels (n=1231 vessels) were post hoc performed by investigators blinded to clinical outcomes. Major adverse cardiovascular events occurred in 99 patients (12.5%). Angiography-derived FFR with an optimal cutoff value of 0.89 for postinterventional culprit vessels and 0.85 for non-culprit vessels emerged as independent predictor of major adverse cardiovascular events after ACS (nonculprit arteries: adjusted odds ratio, 3.78 [95% CI, 2.21-6.45], P<0.001 and post-PCI culprit arteries: adjusted odds ratio, 3.60 [95% CI, 2.09-6.20], P<0.001)[13].

Recently, a retrospective post hoc Angiography-derived FFR analysis of untreated nontarget vessels (any degree of diameter stenosis [DS]) was performed from the randomized multicentre COMFORTABLE AMI (Comparison of Biolimus Eluted From an Erodible Stent Coating With Bare Metal Stents in Acute ST-Elevation Myocardial Infarction) trial by assessors blinded for clinical outcomes. The primary end point was cardiac death, spontaneous nontarget vessel myocardial infarction, and clinically indicated nontarget vessel revascularization (ie, ≥70% DS by 2-dimensional quantitative coronary angiography or ≥50% DS and ischemia) at 5 years. Of 1161 patients with ST-segment-elevation myocardial infarction, 946 vessels in 617 patients were analyzable by Angiography-derived FFR. At 5 years, the rate of the primary end point was significantly higher in patients with Angiography-derived FFR ≤0.80 (n=35 patients, n=36 vessels) versus Angiography-derived FFR >0.80 (n=582 patients, n=910 vessels) (62.9% versus 12.5%, respectively; hazard ratio [HR], 7.33 [95% CI, 4.54-11.83], P<0.001), driven by higher rates of nontarget vessel myocardial infarction (12.8% versus 3.1%, respectively; HR, 4.38 [95% CI, 1.47-13.02], P=0.008) and nontarget vessel revascularization (58.6% versus 7.7%, respectively; HR, 10.99 [95% CI, 6.39-18.91], P<0.001) with no

significant differences for cardiac death. Multivariable analysis identified Angiography-derived FFR ≤0.80 but not ≥50% DS by 3-dimensional quantitative coronary angiography as an independent predictor of the primary end point. Results were consistent, including only >30% DS by 3-dimensional quantitative coronary angiography[14].

In conclusion, Angiography-derived FFR evaluation is feasible in STEMI setting and its value is associated with long-term outcome.

2.6 FAVOR III: Angiography-derived FFR utilization significantly reduces MI vs angio-guided revascularization

Angio-guided revascularization was the strategy utilized in the COMPLETE trial and recent other trials questioned the superiority of invasive physiology through FFR over the traditional angio-based eyeballing[15,16]

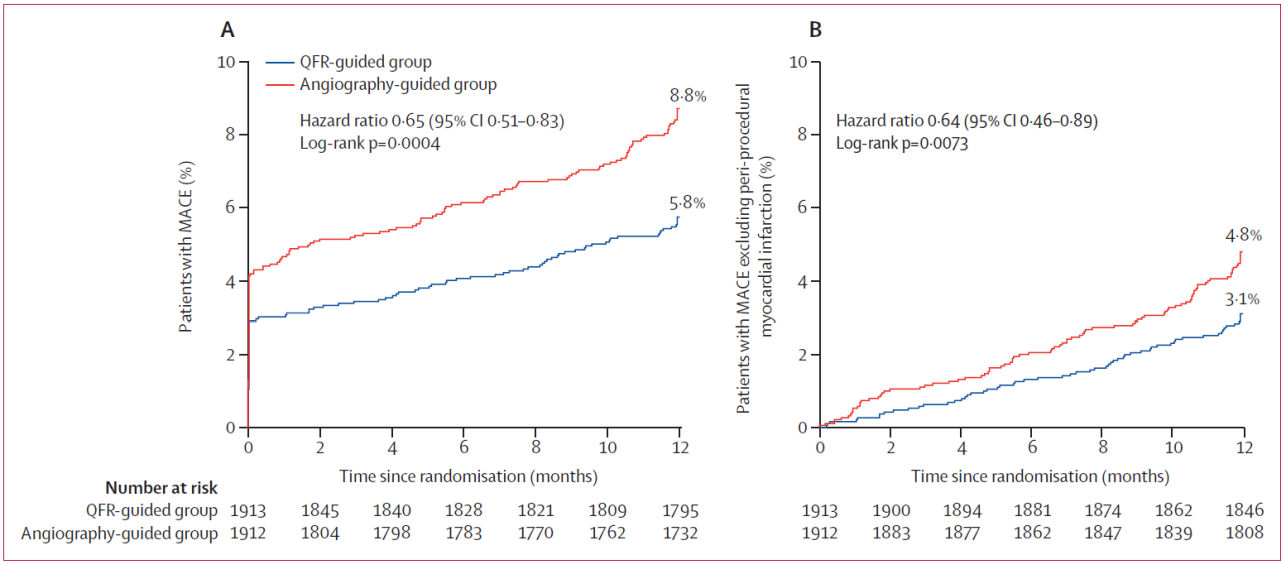


Figure 2: **Kaplan-Meier curves for the primary (A) and major secondary (B) endpoints in the intention-to-treat population**
MACE=major adverse cardiac events. QFR=quantitative flow ratio.

Interestingly, contemporaneously The Comparison of Quantitative Flow Ratio Guided and Angiography Guided Percutaneous Intervention in Patients with Coronary Artery Disease (FAVOR III China) trial compared Angiography-derived FFR-based revascularization versus angio-guided strategy in a multicenter, blinded, randomized, sham-controlled trial done at 26 hospitals in China.

Patients who had at least one lesion with a diameter stenosis of 50–90% in a coronary artery with a reference vessel of at least 2·5 mm diameter by visual assessment were eligible. Patients were randomly assigned to a Angiography-derived FFR-guided strategy (PCI performed only if Angiography-derived FFR ≤0·80) or an angiography-guided strategy (PCI based on standard visual angiographic assessment). Participants and clinical assessors were masked to treatment allocation. Overall, 3847 patients were enrolled and 2428 (63·5%) presented with an acute coronary syndrome. The 1-year primary endpoint occurred in 110 (Kaplan-Meier estimated rate 5·8%) participants in the Angiography-derived FFR-guided group and in 167 (8·8%) participants in the angiography-guided group (difference, –3·0% [95% CI –4·7 to –

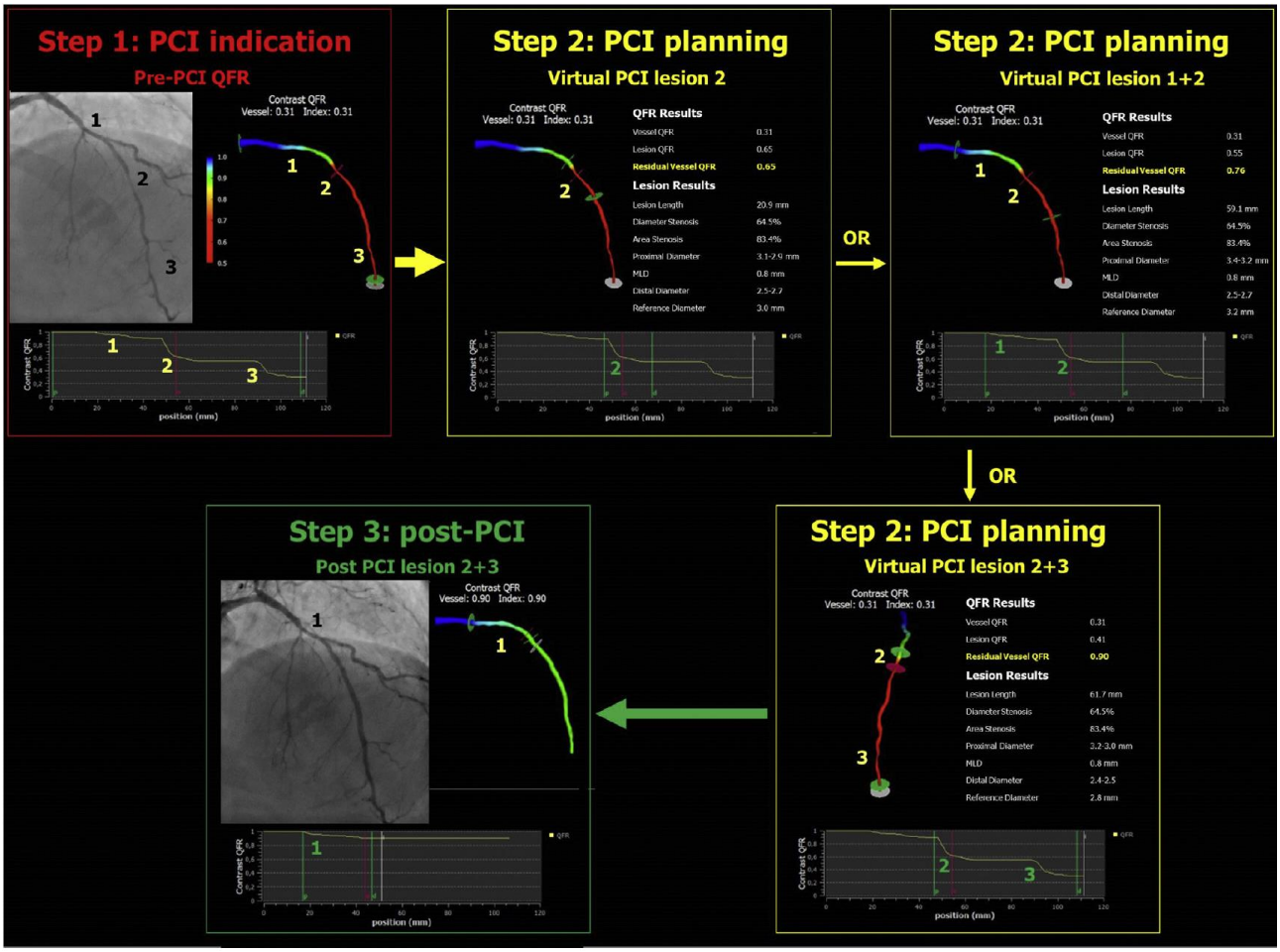
1·4]; hazard ratio 0·65 [95% CI 0·51 to 0·83]; p=0·0004), driven by fewer myocardial infarctions and ischaemia-driven revascularizations in the Angiography-derived FFR-guided group than in the angiography-guided group.

The highly significant reduction in MI was related to both stent-related events in non-flow limiting lesions that were stented in the angio-guided group as well as to flow-limiting lesions that were left untreated because of eyeballing.

2.7 AQVA trial: Angiography-derived FFR virtual PCI vs angio-guided PCI

Physiology is not only a good gatekeeper to indicate PCI, but also a predictor of adverse events when performed after PCI[5]. However, while physiology utilization before PCI is low, after PCI is almost zero.

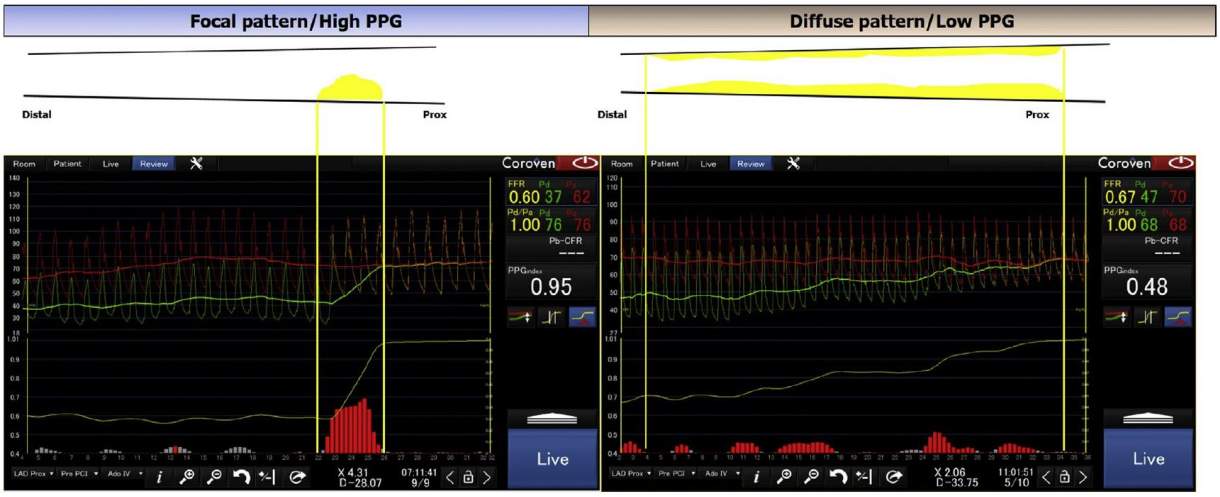
In the recent ERIS (Evolving Routine Standards of FFR Use) study, post-PCI FFR was utilized in less than 10% of lesions investigated with physiology pre-PCI[17]. Most interestingly, even when FFR result after PCI was suboptimal, in 79% of the cases no further action was performed[17]. Reasons for the low use of functional assessment post-PCI and for subsequent intervention are manifold. First, physiology is actually used after PCI only in cases where it was utilized pre-PCI. Second, randomized clinical trials (RCT) addressing the use of FFR to assess PCI results have not been performed, therefore clear instructions and cutoffs for its use are lacking. Third, the need to administer adenosine several times during the same procedure results in increased procedure time, cost and adverse side effects. Fourth, in case of a post-PCI suboptimal functional result, it may be difficult to ascertain the underlying cause. Fifth, reproducibility of physiologic measurements can be challenging in the post-PCI setting and operator's experience significantly impacts on the reliability of the assessment.



Angiography-guided PCI optimization is still the most utilized approach in clinical practice. For this reason, the next step in terms of physiology-guided PCI optimization should be conducting a randomized controlled trial (RCT) comparing physiology- vs conventional angiography-guided PCI optimization adequately powered for hard clinical endpoint.

A full physiology-guided procedure is theoretically possible thanks to the virtual PCI tools that are already available for iFR, Angiography-derived FFR and FFR_{CT} . Recently, the ability of FFR to discriminate pathophysiological patterns of CAD using coronary pressure pullback has been prospectively evaluated[18].

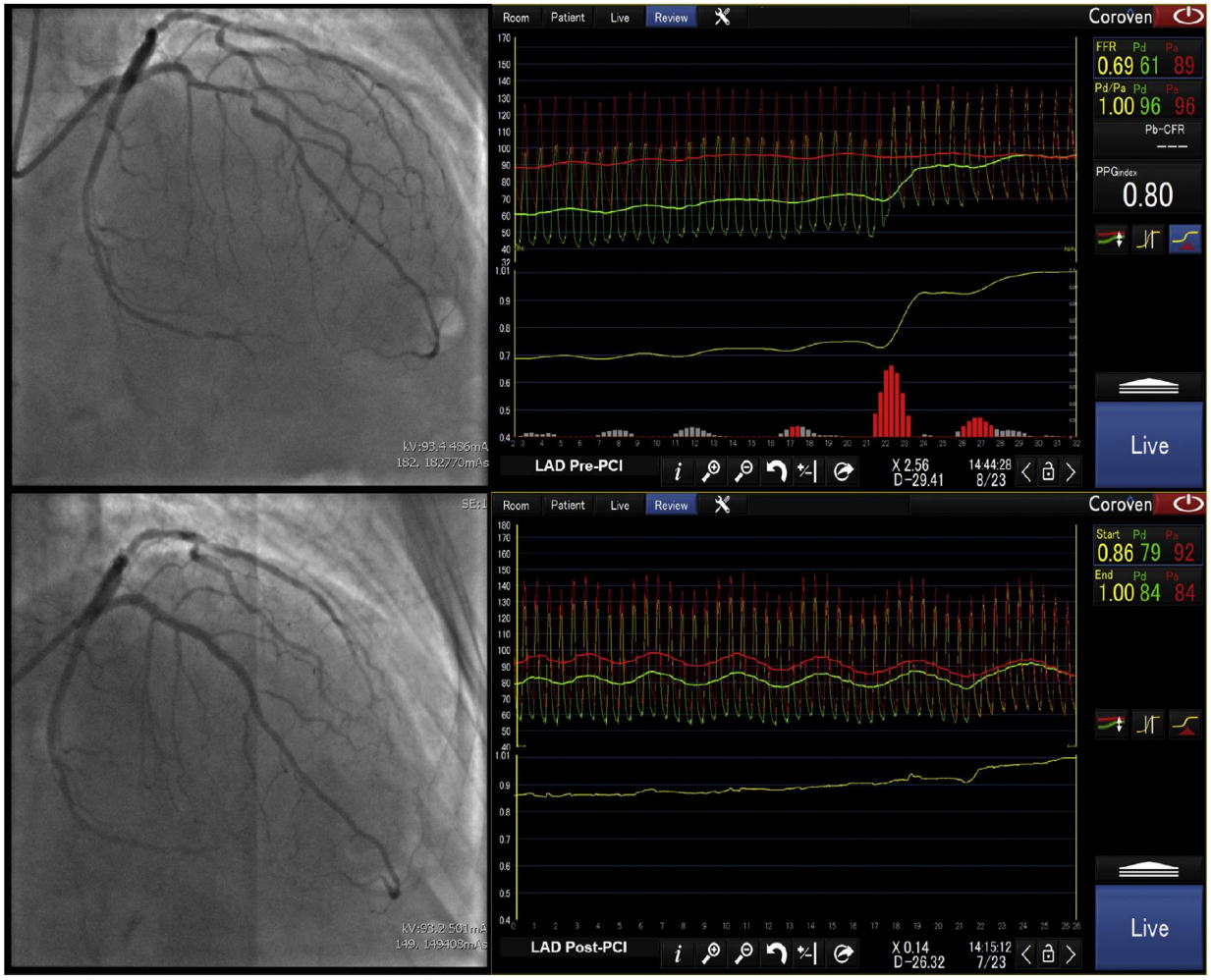
FIGURE 4 **Examples of Different Pre-Percutaneous Coronary Intervention FFR Traces With PPG Index According to Underlying Coronary Artery Disease Mechanisms (High PPG/Focal Disease, Low PPG/Diffuse Disease)**



Yellow lines delimit the diseased portion of the vessel. PPG = pull back pressure gradient; Prox = proximal.

The authors proposed a quantitative assessment, namely the pullback pressure gradients index (PPG index), to discriminate between focal and diffuse disease. The PPG index is a continuous metric with values close to 0 indicating diffuse disease, whereas those close to 1 are suggestive for focal disease and useful in the pre-PCI setting to predict post PCI vessel FFR. However, a limitation of this technique is the necessity of a motorized system for FFR pullback and prolonged adenosine infusions[18]. A new online automatic evaluation of the PPG index with manual pullback will be soon available to overcome this limitation.

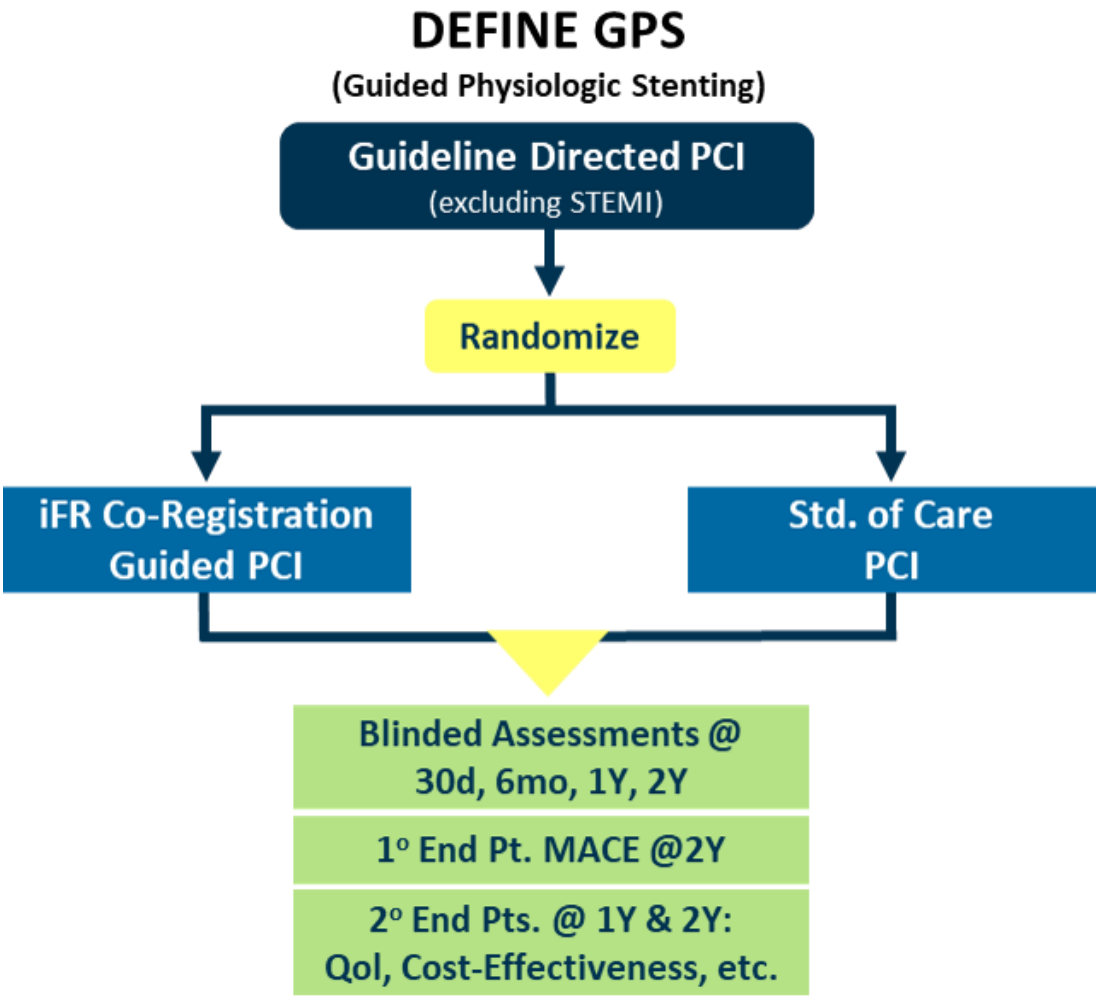
FIGURE 5 **Illustrative Case of Virtual PCI With FFR and PPG Index**



The **top panel** shows a severe angiographic lesion in the mid segment of the left anterior descending coronary artery with an fractional flow reserve (FFR) value in the distal vessel of 0.69. In the **right top panel**, a manual FFR pull back tracing is shown (Coroventis Research, Uppsala, Sweden). The **red bars** depict pressure drops by millimeter. An important drop was identified in the mid segment of the vessel. The functional pattern of coronary artery disease (CAD) was quantified by the pull back pressure gradient (PPG) index of 0.80 (i.e., predominant focal functional CAD). In the **bottom panel**, the results after percutaneous coronary intervention (PCI) are shown. FFR post-PCI was 0.86, and the pull back identified a small pressure step up followed by diffuse pressure losses in the distal segment.

These tools enable not only to obtain a single physiologic value to determine the need of PCI, but also a full physiologic map of the vessel with a point-by-point detailed information of the functional impact of a given stenosis. In addition, it is possible to simulate the treatment of one or more lesions (virtual PCI) in order to estimate the final functional value post-PCI. Functional assessment can be easily checked also after PCI and eventually guide further optimization. The final goal is to achieve an optimal physiologic result in all procedures. Seminal experiences of virtual PCI have been recently published[19]. A validation of virtual intervention with pre-PCI iFR pullback has been performed in serial lesions and diffuse CAD in 32 coronary arteries by Nijjer et al [20]. Obviously, the results of these proof-of-concept studies are only hypothesis generating, but they pave the way for future studies comparing physio-guided virtual PCI with conventional angio-guided PCI. To this end, co-registration of angiographic, imaging and physiological information could have an additional value for PCI optimization[21]. The Distal Evaluation of Functional Performance With

Intravascular Sensors to Assess the Narrowing Effect: Guided Physiologic Stenting (DEFINE GPS) will randomize more than 3000 patients to evaluate patient outcomes of PCI guided by an integrated co-registration platform, which aggregates data of an instant iFR measurement and the angiogram compared against the current standard of care treatment guided by an angiogram alone (NCT04451044).



The same approach is currently tested with Angiography-derived FFR in the Angio-based Quantitative flow ratio Virtual PCI versus Conventional Angio-guided PCI in the achievement of an optimal post-PCI Angiography-derived FFR the AQVA trial (NCT04664140).

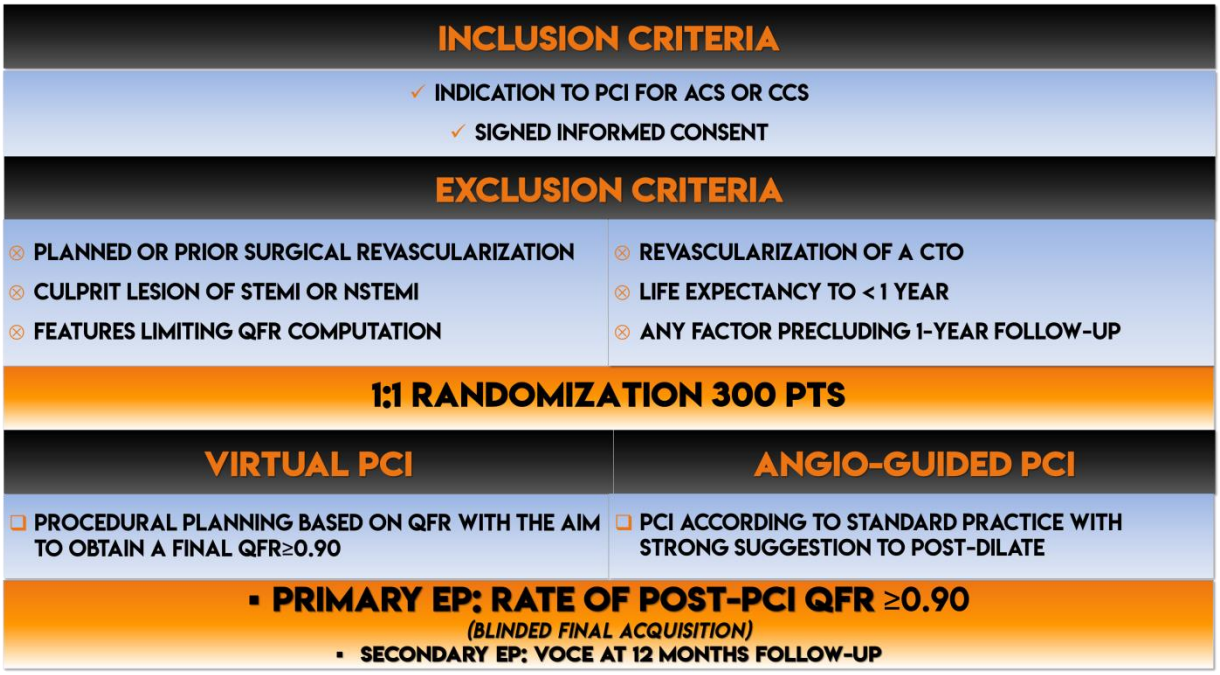
The systematic application of Angiography-derived FFR before stenting to simulate PCI results according to different treatment strategies (virtual PCI) would be an interesting alternative to achieve a fully physiology guided procedure.

The advantages of a virtual PCI strategy based on Angiography-derived FFR application are:

- Angiography-derived FFR is a simple tool, based on what the operator already performs before PCI (namely two perpendicular angiographic projections) and not requiring wire or adenosine.
- It enables to obtain a full physiologic map of the vessel with a point-by-point detailed information of the functional impact of a given stenosis.

- It is possible to simulate the treatment of one or more lesions (virtual PCI) in order to estimate the final functional value post-PCI.

Then, virtual PCI based on Angiography-derived FFR utilization would not increase procedural time or costs and could obtain an optimal post-PCI physiology result in most cases. The "Angio-based Quantitative flow ratio Virtual PCI versus Conventional Angio-guided PCI in the achievement of an optimal post-PCI Angiography-derived FFR" (AQVA) trial is the first step toward this direction and will be the basis for a bigger study focused on hard clinical endpoints.



The trial is randomizing 300 patients to Angiography-derived FFR-guided virtual PCI versus a conventional angio-guided strategy with the aim to achieve a post-PCI Angiography-derived FFR ≥0.90 (blinded assessment).

2.8 Can Angiography-derived FFR overcome FLOWER-MI limitations?

The main limitation of the FLOWER-MI trial are: the dilution of FFR deferral by performing a second procedure in all patients and the inability to perform FFR before PCI in 16% of patients and after in 82% of cases. Angiography-derived FFR could overcome all these limitations. In fact, Angiography-derived FFR projections could be acquired during primary PCI and, in case of negative assessment, the patient can avoid a staged procedure. In addition, a virtual PCI plan based on Angiography-derived FFR "pullback" trace can enable operators to obtain a functionally optimized result without the need to repeat the assessment after PCI.

2.9 Novel angiographic measures of plaque composition and vulnerability

Different methods aimed at the estimation of plaque composition and vulnerability have been developed. They are all based on analyses performed on angiography.

2.9.1 Wall shear stress (WSS)

Wall shear stress (WSS) has been associated with atherogenesis and plaque progression. The present study assessed the value of WSS analysis derived from conventional coronary angiography to detect lesions culprit for future myocardial infarction (MI). Three-dimensional quantitative coronary angiography (3DQCA), was used to calculate WSS and pressure drop in 80 patients. WSS descriptors were compared between 80 lesions culprit of future MI and 108 non-culprit lesions (controls).

Endothelium-blood flow interaction was assessed by computational fluid dynamics (10.8±1.41 min per vessel). Median time between baseline angiography and MI was 25.9 (21.9-29.8) months. Mean patient age was 70.3±12.7. Clinical presentation was STEMI in 35% and NSTEMI in 65%. Culprit lesions showed higher percent area stenosis (%AS), translesional vFFR difference (ΔvFFR), time-averaged WSS (TAWSS) and topological shear variation index (TSVI) compared to non-culprit lesions ($p<0.05$ for all). TSVI was superior to TAWSS in predicting MI (AUC-TSVI=0.77, 95%CI 0.71-0.84 vs. AUC-TAWSS=0.61, 95%CI 0.53-0.69, $p<0.001$). The addition of TSVI increased predictive and reclassification abilities compared to a model based on %AS and ΔvFFR (NRI=1.04, $p<0.001$, IDI=0.22, $p<0.001$).

Conclusions: A 3DQCA-based WSS analysis was feasible and can identify lesions culprit for future MI. The combination of area stenoses, pressure gradients and WSS predicted the occurrence of MI. TSVI, a novel WSS descriptor, showed strong predictive capacity to detect lesions prone to cause MI.

2.9.2 Radial Wall Strain (RWS)

The lipid-to-cap ratio (LCR) and thin-cap fibroatheroma (TCFA) derived from optical coherence tomography (OCT) are indicative of plaque vulnerability.

Aims: We aimed to explore the association of a novel method to estimate radial wall strain (RWS) from angiography with plaque composition and features of vulnerability assessed by OCT.

Methods: Anonymised data from patients with intermediate stenosis who underwent coronary angiography (CAG) and OCT were analysed in a core laboratory. Angiography-derived RWSmax was computed as the maximum deformation of lumen diameter throughout the cardiac cycle, expressed as a percentage of the largest lumen diameter. The LCR and TCFA were automatically determined on OCT images by a recently validated algorithm based on artificial intelligence.

Results: OCT and CAG images from 114 patients (124 vessels) were analysed. The average time for the analysis of RWSmax was 57 (39-82) seconds. The RWSmax in the interrogated plaques was 12% (10-15%) and correlated positively with the LCR ($r=0.584$; $p<0.001$) and lipidic plaque burden ($r=0.411$; $p<0.001$), and negatively with fibrous cap thickness ($r= -0.439$; $p<0.001$). An RWSmax >12% was an angiographic predictor for an LCR >0.33 (area under the curve [AUC]=0.86, 95% confidence interval [CI]: 0.78-0.91; $p<0.001$) and TCFA (AUC=0.72, 95% CI: 0.63-0.80; $p<0.001$). Lesions with RWSmax >12% had a higher prevalence of TCFA (22.0% versus 1.5%; $p<0.001$), thinner fibrous cap thickness (71 µm versus 101 µm; $p<0.001$), larger lipidic

plaque burden (23.3% versus 15.4%; p<0.001), and higher maximum LCR (0.41 versus 0.18; p<0.001) compared to lesions with RWSmax ≤12%.

Conclusions: Angiography-derived RWS was significantly correlated with plaque composition and known OCT features of plaque vulnerability in patients with intermediate coronary stenosis.

3 RATIONALE

After the COMPLETE trial[2], the actual standard of care in the management of STEMI patients with MVD is complete revascularization based on angiography. However, this approach may lead to over- or under-estimation of lesions in a relevant portion of patients with negative impact on prognosis. Invasive physiology has been consistently shown to be superior if compared to angio-guided strategy, but it is underutilized in clinical practice mainly due to feasibility issues.

A functional coronary angiography could overcome the applicability issues related to invasive physiology. In addition, it is particularly appealing in the evaluation of non-culprit lesions since:

a) It is possible to acquire projection during primary PCI and perform the analysis off-line
b) In case of negative assessment, the patient can avoid a second procedure to invasively measure physiology
c) It is possible to optimize most of the procedures by the physiological standpoint through the utilization of the virtual-PCI planner tool pre-PCI without the need to repeat physiology after PCI.
d) It has been recently shown that if compared to an angio-guided approach, Angiography-derived FFR was able to reduce the incidence of spontaneous MI by 36%

Therefore, a strategy based on functional coronary angiography to indicate and guide PCI could be superior if compared to an angio-guided strategy both from the efficacy (CV death, cerebrovascular accident, MI and ischemia-driven revascularization) and from the safety (BARC 3-5, contrast-associated acute kidney injury) standpoint.

4 STUDY ENDPOINTS

4.1 Primary efficacy endpoint

- Cumulative occurrence of all-cause mortality, cerebrovascular accident, reinfarction, or ischemia-driven revascularization

To test if a complete revascularization based on functional coronary angiography to indicate and guide PCI is superior to an angio-based strategy in the reduction of all-cause mortality, cerebrovascular accident, reinfarction, or ischemia-driven revascularization

4.2 Secondary efficacy endpoints

- CV death and reinfarction (prespecified endpoint for the merged analysis with similar ongoing RCTs on the topic)
- CV death, reinfarction and ischemia-driven revascularization (prespecified endpoint for the merged analysis with similar ongoing RCTs on the topic)
- CV death, cerebrovascular accident, or reinfarction (prespecified endpoint for the merged analysis with similar ongoing RCTs on the topic)
- All-cause mortality
- Cerebrovascular accident
- Ischemic stroke
- Ischemia-driven revascularization
- CV death
- Non-fatal MI
- Spontaneous MI
- Periprocedural MI
- Non-culprit vessel oriented composite endpoint (VOCE) as defined as cardiovascular (CV) death, MI or non-culprit target vessel revascularization (TVR)

4.3 Primary safety objective

- Cumulative occurrence of contrast-associated acute kidney injury and bleeding BARC 3-5

To test if a complete revascularization based on functional coronary angiography to indicate and guide PCI is superior to an angio-based strategy in the reduction of BARC 3-5 and contrast-associated acute kidney injury

4.4 Exploratory endpoints

- Quality of life measured with EQ-5D quality of life scale
- Angina symptoms control measured with Seattle Angina Questionnaire (SAQ) Frequency scale
- Quality Adjusted Life Years (QALYs)
- Cost effectiveness and cost utility

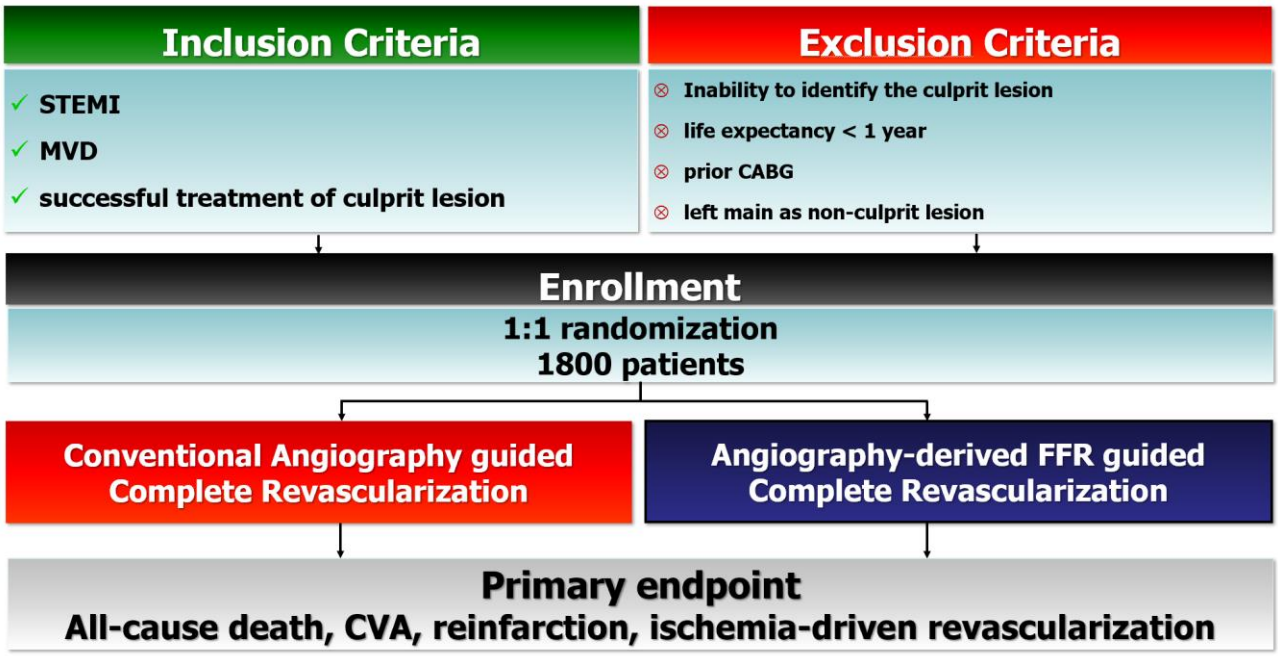
- Number of repeated procedures during index hospitalization

5 STUDY DESIGN, SCREENING AND RANDOMIZATION

5.1 Study design

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

5.2 Study flow chart



5.3 Screening

All patients undergoing CAA because of STEMI 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. Successful culprit lesion treatment must be obtained in all patients before randomization. Screening, eligibility and randomization must be performed within 48 hours from the primary PCI and successful treatment of culprit lesion. After eligibility is confirmed, written informed consent must be obtained prior to randomization. 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.

5.4 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 (male vs. female), age (≤75 years vs. >75 years) and non-culprit vessel location (left

anterior descending artery vs. non left anterior descending artery). 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.

5.5 Measures to minimize/avoid bias

The trial is open-label. Despite the obvious benefits of a doble-blind design, the indication to proceed with angiography-derived FFR or not cannot be concealed to the operator nor to the patient. An independent Clinical Event Committee (CEC) will adjudicate all endpoints. The CEC members and the CEC management team will be completely blinded to the randomization, as well as patient identifying information. The CEC will adjudicate the events based on pre-determined definitions outlined below. Other measures to avoid or minimize bias introduced by the open-label design will include intent-to-treat principles of analysis and use of objective measures for endpoint classification.

6 STUDY POPULATION

6.1 Inclusion criteria

1. STEMI with indication to invasive management **AND**
2. 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**
3. Successful treatment of culprit lesion

6.2 Exclusion criteria

1. Planned surgical revascularization
2. Left main as non-culprit lesion
3. Non-cardiovascular co-morbidity reducing life expectancy to < 1 year
4. Any factor precluding 1-year follow-up
5. Prior Coronary Artery Bypass Graft (CABG) Surgery
6. Impossibility to identify a clear culprit lesion
7. Presence of a chronic total occlusion (CTO)

7 STUDY PROCEDURES

7.1 General information regarding revascularization

Second generation drug eluting stents (DES) must be implanted. All patients must be treated with low dose ASA and a P2Y12 inhibitor (ticagrelor or prasugrel 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.

7.2 Conventional angiography guided complete revascularization

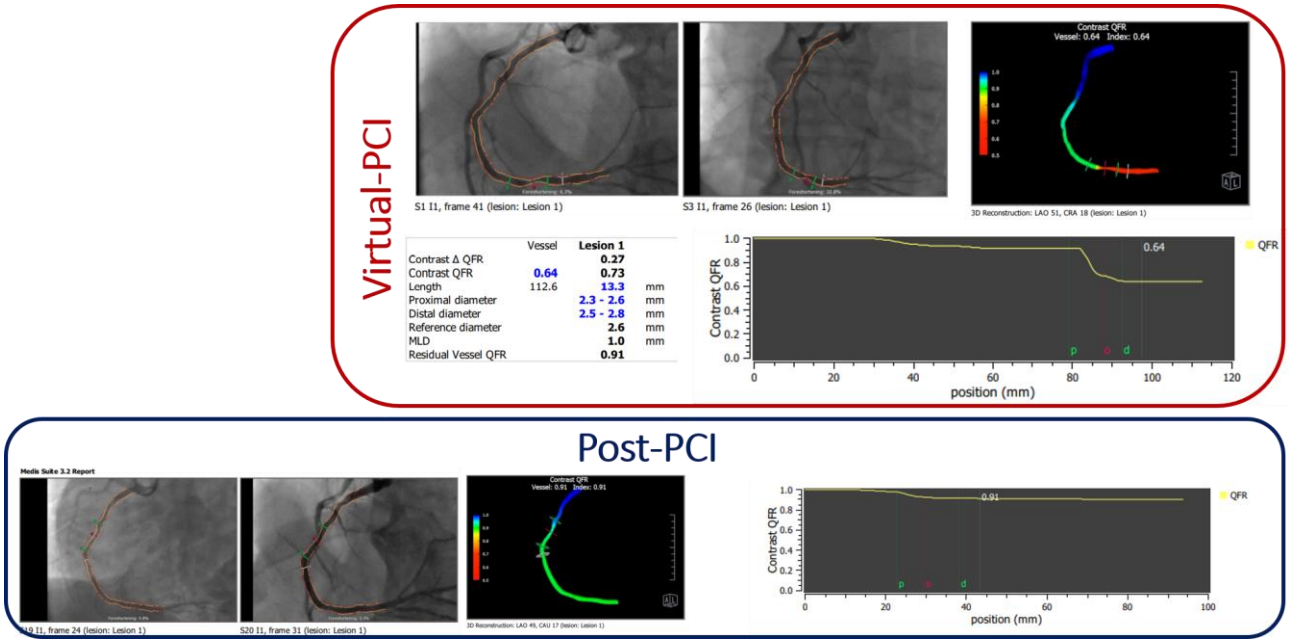
All patients randomized to angio-guided revascularization must undergo PCI of all non-culprit lesions angiographically deemed ≥50%. Complete revascularization must be obtained within index hospitalization.

7.3 Functional coronary angiography complete revascularization

Patients who are randomized to this strategy will receive revascularization of the culprit lesion and functional coronary angiography evaluation on all non-culprit lesions (angiographically deemed ≥50%) and revascularization of all-functional positive lesions according to angio-FFR based virtual PCI plan. Functional evaluation is mandatory for all stenosis. When angiography-derived FFR is not feasible with any of the available tools, then a staged procedure to perform invasive FFR is mandatory. According to available literature, the overall rate of invasive FFR should not exceed 5% of the patients. PCI of vessel with negative functional evaluation is considered a protocol violation. Revascularization of the positive (at angiography-derived FFR assessment) non-culprit lesions must be performed within the index hospitalization.

7.3.1.1 Virtual PCI plan

The virtual PCI plan must be obtained in all patients with positive functional assessment. The aim of the plan is to obtain a final Angiography-derived FFR value ≥0.90. The residual vessel Angiography-derived FFR tool can be utilized to this end.



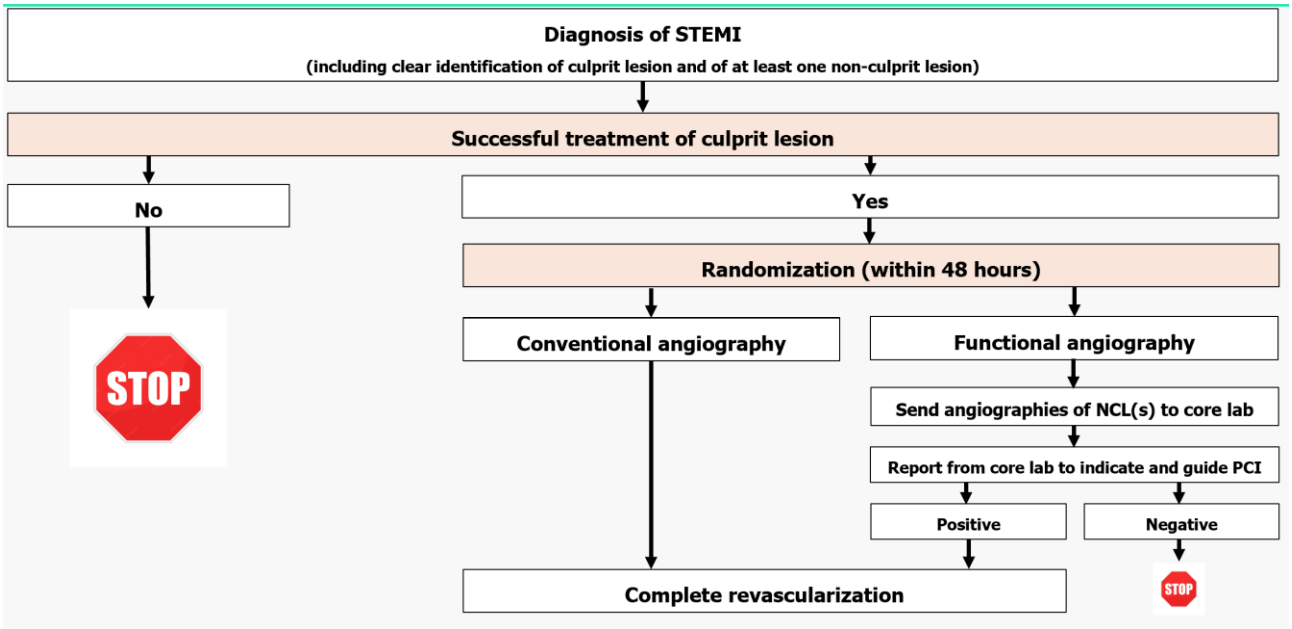
Virtual PCI. Quantitative flow ratio (Angiography-derived FFR) is used as a gatekeeper for percutaneous coronary intervention (PCI). The Angiography-derived FFR analysis shows 1 focal pressure step-down in the distal right coronary artery (RCA). Tt is possible to plan different treatment strategies ("virtual PCI") obtaining the "residual vessel Angiography-derived FFR," which is the Angiography-derived FFR value once the segment between p and d (in green in the Angiography-derived FFR traces) is treated. P and d can be decided and moved by the operator to obtain different post-PCI scenarios. In the example above, residual vessel Angiography-derived FFR would be 0.91 treating lesion 1, resulting in an optimal functional post-PCI result, then confirmed with an actual post-PCI FFR measurement.

7.3.1.2 Angiography-derived measurement of plaque vulnerability

In patients randomized to the AIR strategy with negative FFR, a further stratification of NCLs will be performed. Vessels with an angiography-derived measurement of plaque vulnerability above the validate thresholds (RWSmax >12% or TSVI ≥40.5 m^{-1}) will receive PCI whereas those below the threshold will be treated with optimal medical therapy (OMT).

7.4 Index coronary angiography and functional assessment

The initial angiogram and PCI for the index and eventual staged CAA and PCI in all patients should be recorded, anonymized and maintained locally for shipment to the angiographic and functional core lab (CD, DVD or digital files are acceptable). Regarding the patients randomized to functional coronary angiography complete revascularization (experimental arm), the investigators within 24-48 hours from randomization must send to core lab the recorded and anonymized angiographies of non-culprit vessels. This will allow to the core lab to perform the analysis and to re-send to investigators the report with the indication to proceed or not to revascularization and the eventual procedural plan within 12-24 hours.



7.5 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 or Prasugrel 60 mg loading dose then Ticagrelor 90 mg po BID or Prasugrel 10 mg die unless contraindicated. DAPT duration is as for Institutional protocols. In high bleeding risk patients, namely those with one of the following criteria (at least one major or two minor criteria):

Table 3 Major and minor criteria for hbr at the time of PCI

Major	Minor
	Age ≥75 y
Anticipated use of long-term oral anticoagulation*	
Severe or end-stage CKD (eGFR <30 mL/min)	Moderate CKD (eGFR 30–59 mL/min)
Hemoglobin <11 g/dL	Hemoglobin 11–12.9 g/dL for men and 11–11.9 g/dL for women
Spontaneous bleeding requiring hospitalization or transfusion in the past 6 mo or at any time, if recurrent	Spontaneous bleeding requiring hospitalization or transfusion within the past 12 mo not meeting the major criterion
Moderate or severe baseline thrombocytopenia† (platelet count <100 × 109/L)	
Chronic bleeding diathesis	
Liver cirrhosis with portal hypertension	
	Long-term use of oral NSAIDs or steroids
Active malignancy‡ (excluding nonmelanoma skin cancer) within the past 12 mo	
Previous spontaneous ICH (at any time)Previous traumatic ICH within the past 12 moPresence of a bAVMModerate or severe ischemic stroke§ within the past 6 mo	Any ischemic stroke at any time not meeting the major criterion
Nondeferrable major surgery on DAPT	
Recent major surgery or major trauma within 30 d before PCI	

bAVM indicates brain arteriovenous malformation; CKD, chronic kidney disease; DAPT, dual antiplatelet therapy; eGFR, estimated glomerular filtration rate; HBR, high bleeding risk; ICH, intracranial hemorrhage; NSAID, nonsteroidal anti-inflammatory drug; and PCI, percutaneous coronary intervention.
*This excludes vascular protection doses.[42]
†Baseline thrombocytopenia is defined as thrombocytopenia before PCI.
‡Active malignancy is defined as diagnosis within 12 months and/or ongoing requirement for treatment (including surgery, chemotherapy, or radiotherapy).
§National Institutes of Health Stroke Scale score ≥5.

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. Proprotein convertase subtilsin-kexin type 9 (PCSK9) inhibitors should be utilized to meet the LDL target if otherwise not possible.
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 and heart failure, consideration should be given to administration of an aldosterone antagonist and sodium-glucose Cotransporter-2 (SGLT2) Inhibitors.

7.6 Data collection and Case Report Form

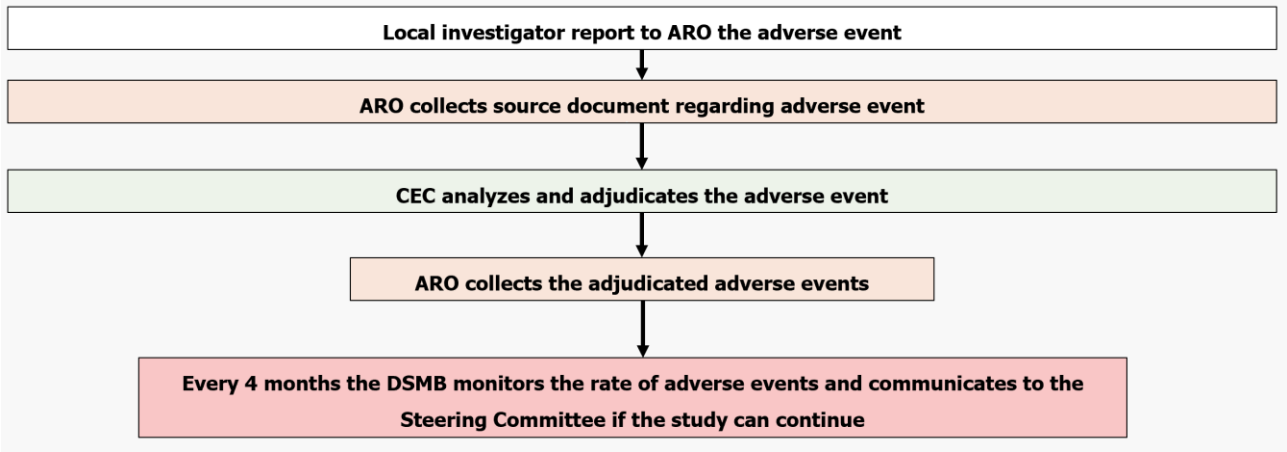
The study investigators will be monitored for consecutive recruitment of patients. A registry of excluded patients will be updated monthly and if selection bias is noticed, it would lead to the exclusion of the centre from the investigation. Data will be collected in electronic case report forms (eCRF). The eCRF will be web-based and all investigators will receive specific credentials for the access. The eCRF will also include the web-based tool for randomization. The quality of the data included in the eCRF will be reviewed by the Academic Research Organization (ARO) of the University Hospital of Ferrara. The eCRF will contain a dedicated tool for reporting adverse events.

7.7 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 5 years. At each visit, clinical outcomes, compliance with medical therapy and smoking cessation, will be assessed. LDL, blood pressure and glycemic targets, anginal status (SAQ), quality of life (EQ-5D) will be assessed at the 12-month and 5 year-follow-up visit.

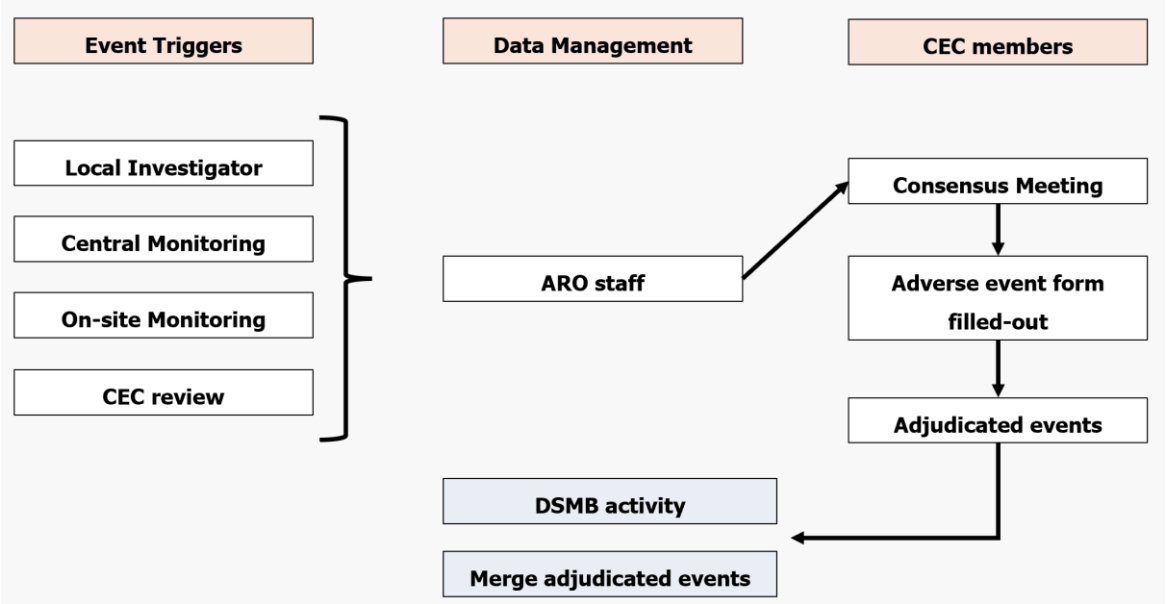
7.8 Study collection of adverse events

All adverse events must be reported by study investigators. The Academic Research Organization will collect the source document of all adverse events. The adverse events will be adjudicated by the Clinical Event Committee (CEC). As reported below, the CEC will transfer to DSMB the adverse events.



7.9 Adjudication of clinical events

A committee consisting of clinicians who are blinded to treatment allocation will adjudicate all adverse events. 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.



7.10 Role of the Data Safety Monitoring Board (DSMB)

The DSMB is responsible for the following items:

- Analysis of the rate of adverse events in the study arms

- Monitoring of study conduction and of the distribution of adverse events between study arms

The DSMB is responsible for immediately stopping the trial if the rate of adverse events would be higher than expected. DSMB will strictly monitor the rate of adverse events in study arms and will communicate to study leadership if the rate of adverse events is higher than expected in one of the study arms. Anyway, the DSMB:

- will generate a report each 4 months illustrating the trend of adverse events (in line with or not with the expectations)
- will communicate each 4 months to the Steering Committee if the study can continue or not.

8 STUDY DEFINITIONS

8.1 Myocardial Infarction (MI)

MI will be defined according to the 4th universal definition of myocardial infarction[22].

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.

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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

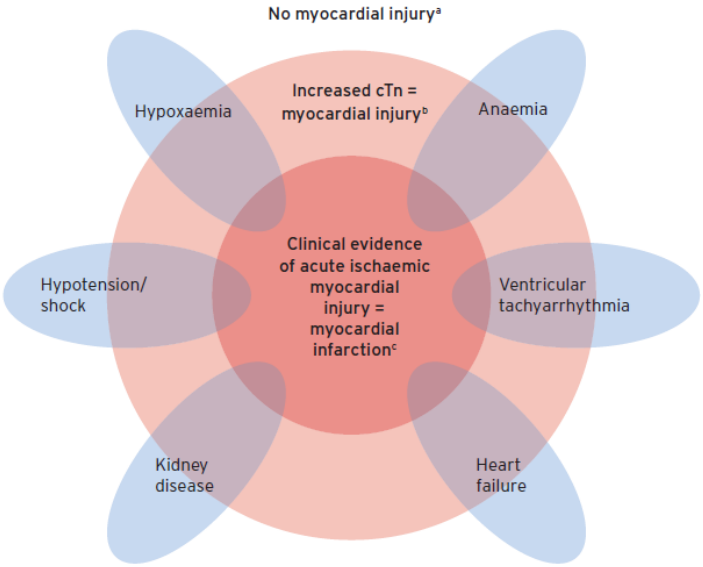
ECG may be normal. The clinical spectrum of NSTE-MI may range from patients free of symptoms at presentation to individuals with ongoing ischemia, electrical or hemodynamic instability or cardiac arrest. The pathological correlate at the myocardial level is cardiomyocyte necrosis. A small proportion 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.

8.1.1 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.

8.1.2 Criteria for myocardial injury

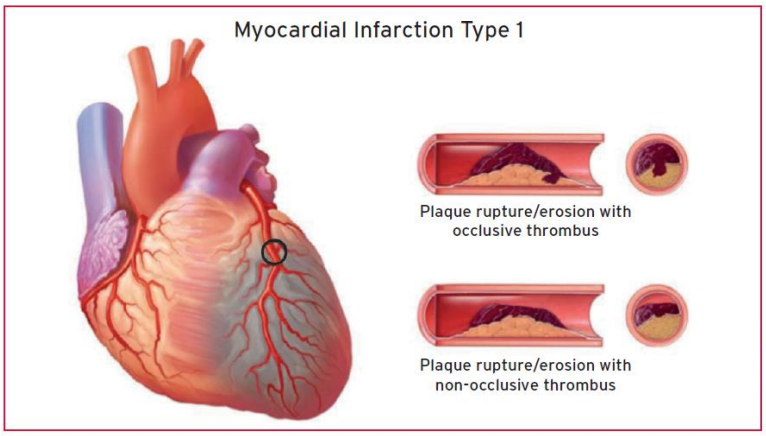
Detection of an elevated cTn value above the 99th percentile URL is defined as myocardial injury. The injury is considered acute if there is a rise and/or fall of cTn values.



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:

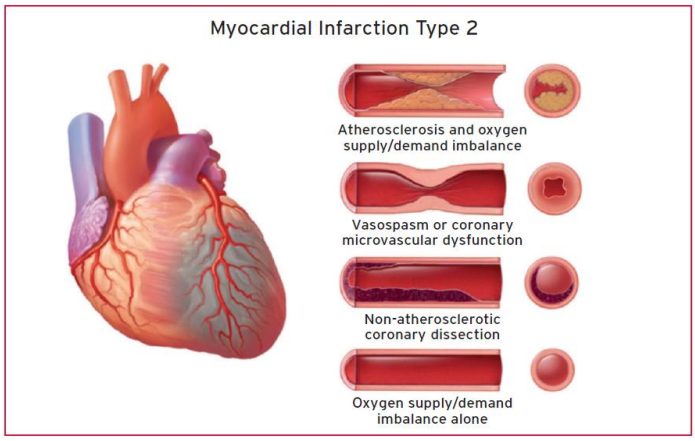
- Symptoms of acute myocardial ischaemia;
- New ischaemic ECG changes;
- Development of pathological Q waves;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology;
- Identification of a coronary thrombus by angiography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

8.1.3 Criteria for spontaneous MI

Spontaneous MI is defined by the presence of acute myocardial injury with clinical evidence of acute myocardial ischemia, with detection of a typical rise and/or fall of cTn values with at least 1 value above the 99th percentile upper reference limit (URL) and at least 1 of the ancillary criteria: symptoms of myocardial ischemia, ischemic ECG changes, pathological Q waves, imaging evidence (e.g., echocardiography), or confirmation of intracoronary thrombus by angiography(including intracoronary imaging) or autopsy[22,23].

8.1.4 Criteria for periprocedural MI

We endorse Fourth Universal MI definition criteria for MI related to PCI complications[22].

Criteria for PCI-related MI ≤48 h after the index procedure (type 4a MI)

Coronary intervention-related MI is arbitrarily defined by an elevation of cTn values more than five times the 99th percentile URL in patients with normal baseline values. In patients with elevated pre-procedure cTn in whom the cTn level are stable (≤20% variation) or falling, the post-procedure cTn must rise by >20%. However, the absolute post-procedural value must still be at least five times the 99th percentile URL. In addition, one of the following elements is required:

- New ischaemic ECG changes;
- Development of new pathological Q waves;[a]
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality 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 a side branch occlusion/thrombus, disruption of collateral flow, or distal embolization.[b]

[a]Isolated development of new pathological Q waves meets the type 4a MI criteria if cTn values are elevated and rising but more than five times the 99th percentile URL.

[b]Post-mortem demonstration of a procedure-related thrombus in the culprit artery, or a macroscopically large circumscribed area of necrosis with or without intra-myocardial haemorrhage meets the type 4a MI criteria.

8.2 Death

Deaths will be classified as cardiovascular, non-cardiovascular or undetermined cause according to ARC-2 criteria[24]. 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.

8.3 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, Angiography-derived FFR≤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.

8.4 Stent Thrombosis

Stent thrombosis will be defined according to ARC-2 criteria[24]. Definition and timing of stent thrombosis:

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.

8.5 Cerebrovascular accident and Stroke

Cerebrovascular accident is the cumulative occurrence of transient ischemic attack (TIA) and stroke. Stroke is 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.

Table 4: Stroke and TIA

Diagnostic criteria
Acute episode of a focal or global neurological deficit with at least one of the following: change in the level of consciousness, hemiplegia, hemiparesis, numbness, or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke
Stroke: duration of a focal or global neurological deficit ≥24 h; OR <24 h if available neuroimaging documents a new haemorrhage or infarct; OR the neurological deficit results in death
TIA: duration of a focal or global neurological deficit <24 h, any variable neuroimaging does not demonstrate a new haemorrhage or infarct
No other readily identifiable non-stroke cause for the clinical presentation (e.g. brain tumour, trauma, infection, hypoglycaemia, peripheral lesion, pharmacological influences), to be determined by or in conjunction with the designated neurologist[a]
Confirmation of the diagnosis by at least one of the following
Neurologist or neurosurgical specialist
Neuroimaging procedure (CT scan or brain MRI), but stroke may be diagnosed on clinical grounds alone
Stroke classification
Ischaemic: an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of the central nervous system tissue
Haemorrhagic: an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid haemorrhage
A stroke may be classified as undetermined if there is insufficient information to allow categorization as ischaemic or haemorrhagic
Stroke definitions[b]
Disabling stroke: an mRS score of 2 or more at 90 days and an increase in at least one mRS category from an individual's pre-stroke baseline
Non-disabling stroke: an mRS score of <2 at 90 days or one that does not result in an increase in at least one mRS category from an individual's pre-stroke baseline

mRS: modified Rankin Scale.
[a]Patients with non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence of cerebral infarction-based upon neuroimaging studies (CT scan or brain MRI).
[b]Modified Rankin Scale assessments should be made by qualified individuals according to a certification process [23–25].

8.6 Nonfatal Cardiac Arrest

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

8.7 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

8.8 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.

8.9 Bleeding complications

The bleeding complications will be classified in agreement with the BARC classification

Table 5: Bleeding

Life-threatening or disabling bleeding
- Fatal bleeding *(BARC type 5)* OR
- Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome *(BARC type 3b and 3c)* OR
- Bleeding causing hypovolaemic shock or severe hypotension requiring vasopressors or surgery *(BARC type 3b)* OR
- Overt source of bleeding with drop in haemoglobin ≥5 g/dl or whole blood or packed red blood cells (RBCs) transfusion ≥4 units[a] *(BARC type 3b)*

Major bleeding *(BARC type 3a)*
- Overt bleeding either associated with a drop in the haemoglobin level of at least 3.0 g/dl or requiring transfusion of two or three units of whole blood/RBC, or causing hospitalization or permanent injury, or requiring surgery AND
- Does not meet criteria of life-threatening or disabling bleeding

Minor bleeding *(BARC type 2 or 3a, depending on the severity)*
- Any bleeding worthy of clinical mention (e.g. access site haematoma) that does not qualify as life-threatening, disabling, or major

BARC: Bleeding Academic Research Consortium [29]; RBC, red blood cell.
[a]Given that one *unit* of packed RBC typically will raise the haemoglobin concentration by 1 g/dl, an estimated decrease in haemoglobin will be calculated.

For the current study, the BARC 3-5 will be considered.

In addition, bleeding will be classified as access-site related and as consequence or not of repeated procedure.

9 STATISTICAL ANALYSIS PLAN

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. Correction for multiple testing to account for type I error will be performed according to Holm, and Bretz graphical approaches[25].

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 secondary endpoint by correction for multiple testing according to Holm, and Bretz graphical approaches[25]. 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.

9.1 Determination of sample size

To maximize the possibility to achieve important information, the follow-up will be censored for all patients when the last enrolled patient will achieve the 1-year follow-up. Considering that the recruitment will take around 20-22 months, we will have a median follow-up around 16-18 months, ranging from 12 to 22 months. The estimated occurrence of the primary endpoint according to previous studies is around 9% in the control group. In the FAVOR III China trial, the angiography based FFR strategy was able to reduce the composite primary efficacy endpoint by 35%. Therefore, 1718 patients are required to have a 80% chance of detecting, as significant at the 5% level, a 35% difference in the primary outcome between the two study groups considering a 9% rate of the primary endpoint in the control group. Considering a 5% attrition rate final sample size is inflated to 1800 patients.

10 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.

11 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.

12 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.

13 DATA MERGING

The present study is powered for the POCE, but not for CV death and MI. In order to obtain compelling evidence on this latter endpoint, the data of the present study will be merged with those of RCTs sharing the same inclusion and exclusion criteria, randomization and study interventions.

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 Sponsor has 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 STUDY COMMITTEES

The Study Committees composition is detailed in the appendix.

18.2 ADDRESS LIST

18.2.1 Sponsor

Azienda Ospedaliero Universitaria di Ferrara,

via Aldo Moro 8, 44124 Cona (FE), Italy

18.2.2 Principal Investigator

Doctor Simone Biscaglia

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

Telephone number: +39 0532 239883

18.2.3 Academic Research Organization (ARO)

Cardiology Unit, University Hospital of Ferrara

Via Aldo Moro 8, Cona (FE), Italy

00390532236450

18.3 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.

18.4 FUNDING AND SUPPORT

The project was presented for the call of Ricerca Finalizzata 2021 and obtained the grant by Ministero della Salute (GR-2021-12372516). During the study, to achieve the scientific goal of the study and to allow the coverage of the costs, the Steering Committee can integrate the study budget with further fund raising from private and public companies. The potential achievements will be immediately communicated to Sponsor and Regulatory Agencies (including Ethic Committee). Study supporters have no role in the study design, conduct, and publication of the primary as well as any secondary manuscripts.

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