# PROTOCOL
# COMPARE – ACUTE

## Fractional Flow Reserve guided Primary Multivessel Percutaneous Coronary Intervention to Improve Guideline Indexed Actual Standard of Care for Treatment of ST-elevation Myocardial Infarction in Patients with Multivessel Coronary Disease.

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Final Version C
18/November/2012
Including Amendment 1

# Summary of main changes of the global amendment 1 - 18nov2012
## Amendment to the Protocol_Final version B_16May2011

**Study title: COMPARE – ACUTE**
Fractional Flow Reserve guided Primary Multivessel Percutaneous Coronary Intervention to Improve Guideline Indexed Actual Standard of Care for Treatment of ST-elevation Myocardial Infarction in Patients with Multivessel Coronary Disease.
(Original Protocol: Final version B dated 16May2011)

**Date global amendment 1:** 18 November 2012

**This amendment applies to:** all clinics participating in the Compare-Acute study.

**Main changes of the amendment:**

**Inclusion criteria**

- Upper age limit has been increased to 85 years

**Exclusion criteria**: Two exclusion criteria are added

- STEMI due to in-stent thrombosis
- Complicated IRA treatment, with one or more of the following:
  - Extravasation,
  - Permanent no re-flow after IRA treatment (TIMI flow 0-1),
  - Inability to implant a stent

**In the section trial description the following has been added:**

- ACT assessment before FFR of non-IRA lesions is recommended
- Assessment of left ventricle function or wall motion abnormalities before primary PCI are at discretion of local practice

**In the section definitions / revascularisations the following change is made:**
The staged non-IRA revascularisations can take place until day 45 post primary PCI, in stead of 42 days.

**General**
Some administrative changes have been applied and typing errors have been corrected.

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## Protocol Synopsis

| | |
|---|---|
| **Title:** | Fractional Flow Reserve guided Primary multivessel Percutaneous Coronary Intervention to improve guideline indexed actual standard of care for treatment of ST-elevation Myocardial Infarction in patients with multivessel disease. |
| **Acronym:** | Compare Acute : Comparison between FFR guided revascularization versus conventional strategy in acute STEMI patients with MVD. |
| **Design:** | Prospective, 1: 2 randomisation |
| **Hypothesis:** | FFR-guided complete percutaneous revascularisation of all flow-limiting stenoses in the non-IRA performed within the same procedure as the primary PCI or within the same hospitalisation will improve clinical outcomes compared to the staged revascularisation, guided by prove of ischemia or clinical judgment, as recommended from the guidelines. |
| **Inclusion Criteria**: | All STEMI patients between 18-85 years who will be treated with primary PCI in < 12 h (more than 12 hr if persisting pain allowed) after the onset of symptoms and have at least one stenosis of ≥50% in a non-IRA judged feasible for treatment with PCI. |
| **Key Exclusion Criteria:** | Left main stem disease (stenosis > 50%)<br>STEMI due to in-stent thrombosis<br>Severe stenosis with TIMI flow ≤ II of the non-IRA artery<br>Non-IRA stenosis not amenable for PCI treatment<br>Complicated IRA treatment<br>Killip class III or IV already at presentation or at the end of culprit lesion treatment<br>Intolerance to Aspirin, Clopidogrel, Plasugrel, Ticagrelor, Heparin, Bivaluridin, or Everolimus and known true anaphylaxis to prior contrast media or known bleeding diathesis or known coagulopathy<br>Planned elective surgical procedure necessitating interruption of thienopyridines during the first 6 months post enrolment |
| **Primary endpoint:** | Composite endpoint of all cause mortality, non-fatal Myocardial Infarction, any Revascularisation and Stroke (MACCE) at 12 months |
| **Major Secondary Endpoints:** | Primary endpoint at 24 and 36 months as well as outcomes of each component of the primary endpoint at 12, 24 and 36 months.<br><br>Primary endpoint rates at 12, 24 and 36 months in the subgroup of patients receiving staged or acute PCI treatment |

| | |
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| | for FFR positive lesions in the non-IRA vs the subgroup of patients that received optimal medical treatment though had a FFR positive lesion.<br><br>Primary endpoint rates at 12, 24 and 36 months in the subgroup of patients receiving acute PCI treatment for FFR positive lesions in the non-IRA vs the subgroup of patients receiving staged PCI treatment for FFR positive lesions in the non-IRA.<br><br>Primary endpoint rates 12, 24 and 36 months in the subgroup of patients receiving staged PCI treatment for FFR negative lesions in the non-IRA vs the subgroup of patients not receiving PCI treatment for FFR negative lesions in the non-IRA.<br><br>Composite endpoint of Cardiac death, Myocardial Infarction, any Revascularisation, Stroke and Major bleeding at 12, 24 and 36 months (NACE i.e. Net Adverse Clinical Events). |
| **Sample size:** | A total sample size of 885 patients (286 in the FFR-guided group, 572 in the control group) is needed to obtain a power of at least 80% with a two-sided false positive error rate (alpha) of 5% for rejecting the null-hypothesis of no difference when the endpoint incidence is 8% in the FFR guided group vs 14.5% in the control group, using the Pearson Chi-square test for two proportions assuming an asymptotic normal distribution with a normal approximation method and considering a 3% loss in follow-up. |
| **Follow Up:** | 30 day, 12, 24 and 36 months. (Mail, Phone and out-patient clinic) |

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# List of Abbreviations

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|---|---|
| ACC | American College of Cardiology |
| ACS | Acute Coronary Syndromes |
| AE | Adverse event (see definition in Section 6.4.1) |
| AHA | American Heart Association |
| ASA | Acetylsalicylic Acid (Aspirin) |
| AVB | Atrioventricular Block |
| BID | Twice a day |
| BP | Blood Pressure |
| CABG | Coronary Artery Bypass Graft |
| Cath Lab | Catheterization Laboratory or catheterization room or coronarography room |
| CD | Compact Disc |
| CAD | Coronary artery disease |
| CHD | Coronary Heart Disease |
| CI | Confidence Interval |
| Core Lab | Laboratory for central review for ECG/angiography |
| CRF | Case Report Form (electronic/paper) |
| CSA | Clinical Study Agreement |
| CYP3A | Cytochrome P4503A, the most abundant of the P450 enzymes responsible for initial drug metabolism in the liver |
| DSMB | Data Safety Monitoring Board |
| ECG | Electrocardiogram |
| EC | Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC) |
| Endpoint | Symptomatic or asymptomatic events that are centrally adjudicated and specifically defined in the protocol as efficacy variables. |
| EOT | End of treatment (refers to study visit at which patient is discontinued from study medication) |
| ESC | European Society of Cardiology |
| FFR | Fractional Flow Reserve |
| FUP | Follow UP |
| GCP | Good Clinical Practice |
| GMP | Good Manufacturing Practices |
| GP | Glycoprotein |
| GUSTO | Global Utilization of Streptokinase and t-PA for occluded coronary arteries |
| Hb | Hemoglobin |
| HR | Hazard Ratio |
| IB | Investigator Brochure |
| ICF | Informed Consent Form |

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|---|---|
| ICU | Intensive Care Unit |
| ICH | International Conference on Harmonization |
| ICAC | Independent Central Adjudication Committee |
| IHD | Ischemic Heart Disease |
| IPA | Inhibition of Platelet Aggregation |
| ISTH | International Society on Thrombosis and Haematostasis |
| IVRS/IWRS | Interactive Voice Response System/ Interactive Web Response System |
| IV | Intravenous |
| LBBB | Left Bundle Branch Block |
| LD | Loading Dose |
| LSLV | Last Subject Last Visit |
| LVH | Left Ventricular Hypertrophy |
| MI | Myocardial Infarction |
| NIRA | Non Infarct related artery |
| NSAID | Non Steroidal Anti-Inflammatory Drug |
| NSTEMI | Non ST-Elevation Myocardial Infarction |
| OAE | Other Significant Adverse Event (see definition in Section 11.1.2) |
| PCI | Percutaneous Coronary Intervention |
| PI | Principal Investigator |
| PLATO | A study of PLATelet inhibition and patient Outcome |
| RCT | Randomised Clinical Trial |
| SAE | Serious adverse event (see definition in Section 6.4.2). |
| STEMI | ST-Elevation Myocardial Infarction |
| TIA | Transient Ischemic Attack |
| TIMI | Thrombolysis in Myocardial Infarction |
| TMPG | TIMI Myocardial Perfusion Grade |
| WBDC | Web Based Data Capture |
| WHO | World Health Organization |

## Summary

ST-elevation myocardial infarction (STEMI) is a common and the most severe presentation of ischemic coronary disease. The majority of patients presenting with STEMI show presence of coronary disease beyond the culprit vessel and almost 40-50% will have an angiographic significant stenosis of at least one non infarct related coronary artery (non-IRA).

Evidence shows that patients with STEMI and multivessel disease have a worse outcome in survival compared to those without multivessel disease and that there is a higher rate of post-MI heart failure in patients with multivessel disease, probably due to persistent myocardial ischemia.
Fractional flow reserve (FFR) has become the golden standard in cathlab method for defining flow-limiting coronary lesions requiring mechanical revascularisation in patients with stable angina pectoris. The FFR measurements in non culprit lesions compared to angiographic assessment only have recently been proven to be safe and accurate even in setting of STEMI.

Primary Percutaneous Coronary Intervention (PPCI) has been established as the preferred revascularisation technique for STEMI patients. The actual ESC and AHA/ACC guidelines do not recommend complete revascularisation during primary PCI. However, these recommendations are based on limited and outdated clinical evidence and whether these recommendations hold true in current interventional cardiology practice need to be investigated.

Therefore, a prospective randomised trial in patients with multivessel disease presenting with STEMI to evaluate a strategy of FFR-guided complete revascularisation during primary PCI compared to primary PCI of culprit vessel only followed by staged revascularisation of non-IRA in case of proven ischemia or persistence of symptoms of angina as indicated from the guidelines, in patients with multivessel disease presenting with STEMI, is needed.

Patients will be randomised after successful revascularisation of the culprit vessel. Patients that have at least one lesion with a diameter of stenosis of 50% or more on visual estimation, feasible (operators judgement) for treatment with PCI in a non-IRA, will be randomised either to the FFR guided complete revascularisation arm or to the staged revascularisation by proven ischemia or persistence of symptoms of angina arm. After randomisation a FFR measurement will be performed in all stenosed non-IRA lesions. In the FFR-guided arm, patients will receive a PCI when FFR measurements in a non-IRA lesion will result in a value of less or equal to 0.80.

Hypothesis: Patients who receive FFR-guided complete revascularisation during primary PCI hospitalisation will have a lower rate of major adverse clinical events (MACCE) at 1 year than patients who will only have staged revascularisation in case of proven ischemia or symptoms of angina as indicated by the current ESC/AHA/ACC guidelines.

The study will be performed in elected large volume primary PCI centres in Europe and Asia. A total of 885 patients will be randomised in a 1:2 fashion and with intention to treat. All events after enrolment will be captured through direct correspondence to the patient, checking of patient charts as well as national health system registers. Adjudication of events will be done by an independent clinical event committee and angiographic core lab.
The study is expected to finish enrolment in 3.5 years and produce the first report in 4.5 years after the randomisation of the first patient.

## Background

**ST-elevation myocardial infarction: incidence and management.**

Acute ST elevation myocardial infarction (STEMI) is the clinical manifestation of acute coronary thrombotic occlusion[1,2] STEMI is the most feared acute coronary syndrome as it is associated with higher rates of recurrent MI, arrhythmias, heart failure and death[3].
The WHO estimated in 2002, that 12.6 percent of worldwide deaths arise from ischemic heart disease representing the leading cause of death in developed countries. Presence of another stenosis (> 50%) in at least one other (non-culprit) coronary artery is a common angiographic finding during primary percutaneous coronary intervention (PPCI) for STEMI. The incidence of such finding ranges between 34% [4] to 60% [56].
Acute left ventricular dysfunction followed by left ventricle remodelling are the main mechanisms that lead to heart failure post-MI[7]. The rates of heart failure post MI are higher in patients with multivessel coronary artery disease (CAD) and this might be due to ongoing ischemia due to presence of flow-limiting coronary obstructions in other non-culprit vessels. Therefore it appears logical that complete revascularisation can lead to improved left ventricular function in short and long term follow-up post MI.
The guidelines for percutaneous coronary revascularisation published in 2005[8] recognise the PPCI as the treatment of choice for STEMI. These guidelines support complete revascularisation during

the PPCI only if patients present in cardiovascular shock. In all other situations complete revascularisation during PPCI is not encouraged. Also in the very recent ESC guidelines for the management of acute myocardial infaction in patients presenting with ST-segment elevation (EHJ 2012), the guideline state that in patients with multi-vessel disease, primary PCI should be directed only at the infarct-related coronary artery (IRA, culprit vessel), with decisions about PCI of non-culprit lesions guided by objective evidence of residual ischemia or viability with stress testing and imaging at later follow-up (Class 1A indication). These recommendation are based on only one study[5].

In this study, the results were driven by a higher rate of re-infarctions and target vessel revascularisations at 1 year while no significant difference was observed in survival rates. The endpoint of target vessel revascularisation is very disputable in this setting as it doesn't represent all lesions but only the treated ones. Indeed as shown from the results of this study, in the multivessel treatment cohort the rate of target lesion revascularisation resulted in 25% compared to 15% in the culprit only cohort. However the culprit only cohort required 12 % further surgical revascularisation during the first year while only half this much was needed in the multivessel treatment cohort. Furthermore the percentage of patients who received a staged non-IRA treatment is not shown. By putting this results together the rate of revascularisation will result in (25% + 6% = 31%) in the multivessel cohort versus (15% + 12% = 27% at least) in the culprit-only group suggesting no further significant difference between these groups.
Also, looking at the outcome between multivessel treatment during primary PCI versus staged, no significant difference was observed at one year in mortality while reinfarctions and target vessel revascularisations were significantly lower in the multivessel treatment during the primary procedure. Furthermore, no difference was found between the rate of target vessel revscularization (TVR) and reinfarctions between IRA-only versus multivessel treatment during primary PCI. This study does not represent the current coronary treatment reality as not all patients received a stent. The angioplasty was performed either with bare metal stents (BMS) or plain old balloon-angioplasty (POBA) which might explain the high rate of target vessel revascularisations. Finally this study bears with it all, the limitations of a retrospective cohort analysis.
The recently published new guidelines in coronary revascularisation[9] does not address this issue, probably due to the confounding results of registers and studies that have tried to address this issue in the last decade confirming once more the need of a large randomised trial in this setting. While large retrospective registers[10] show a disadvantage for complete revascularisation during PPCI, small sized prospective randomised trials[4,11] have shown a superiority of this approach mainly due

to the reduction of re-intervention for recurrent angina pectoris. Khattab et al.[11] have shown that complete revascularisation during PPCI resulted in similar safety and efficacy clinical endpoints at one year compared with staged PCI of non IRA and might reduce infarct size. Another prospective randomised trial has shown that complete revascularisation during PPCI versus culprit only was associated with significant improvements in MACE[4]. The results were mainly driven by a reduction on revascularisation rates at one year follow-up.

Results from randomised trials and meta-analysis in STEMI patients have shown that first generation DES results in superior clinical outcomes compared to BMS[12,13,14] The second generation everolimus-eluting stent[1516] and new antithrombotic[17] or anticoagulant regimens have drastically improved procedural and clinical outcomes after PCI. Results from recently published large scale all comer trials have shown that the new second generation DES are extremely safe and effective for treatment of STEMI and have further improved the MACE rates compared to first generation DES in STEMI patients (COMPARE AMI)[18].

## Anticoagulant and antithrombotic regimens in STEMI

**Antiplatelet therapy**

The actual guidelines on revascularisation in STEMI suggest a dual antiplatelet therapy consisting of ASA 150–300 mg per os or 250 (–500) mg bolus i.v., followed by 75–100 mg daily, and prasugrel 60 mg loading dose, followed by 10 mg daily, or ticagrelor 180 mg loading dose, followed by 90 mg twice daily.[19]

Clopidogrel should be used only if the more effective ADP receptor blockers are contraindicated or unavailable. Prasugrel has been proven superior to Clopidogrel (300 mg loading dose, 75 mg maintenance dose) in reducing combined ischemic endpoints and stent thrombosis in STEMI patients without increasing the risk of severe bleeding.[17] A predefined subgroup analysis has demonstrated that STEMI or NSTE-ACS patients referred for PCI significantly benefit from ticagrelor, vs. clopidogrel, with similar bleeding rates.[20] The controversial literature data, the negative outcome of the only prospective RCT,[21] and the beneficial effects of faster acting and more efficacious ADP receptor blockers in primary PCI do not support pre-hospital or pre-catheterization use of GPIIb–IIIa inhibitors.

**Anticoagulation**

Options for anticoagulation include UFH 60 IU/kg i.v. bolus with GPIIb–IIIa inhibitor or UFH 100 IU/kg i.v. bolus without GPIIb–IIIa inhibitor, or bivalirudin 0.75 mg/kg bolus followed by 1.75 mg/kg/h. A recent study suggested bivalirudin monotherapy as an alternative to UFH plus a GPIIb–IIIa inhibitor. Significantly lower severe bleeding rates led to a beneficial net clinical outcome indicating that bivalirudin may be preferred in STEMI patients at high risk of bleeding. One-year outcome of the HORIZONS RCT confirmed the beneficial action of bivalirudin monotherapy vs. UFH and a GPIIb–IIIa inhibitor. In fact, the very recent ESC 2012 STEMI guideline upgraded the recommendation for the use of bivalirudin (with 2b3a blockers only restricted to bailout) over unfarctionated heparin to Class 1B. Unfractionated Heparin (with or without 2b3a blckers) should must be used in patients not receiving bivalirudin or enoxaparin (Class 1 C).

In this perspective it becomes clear that new trials in STEMI should incorporate the guidelines recommendations for antithrombotic and anticoagulant regimens.

Few data are available in the outcome of the combination between plasugrel or ticagrelor with bivalirudin but the actual evidence as well as expert opinion suggest that this might be a very beneficial combination as it theoretically leads to improved safety as plasugrel and/or ticagrelor reduce the acute stent thrombosis rates and bivalirudin reduces the bleeding complications.

Due to this major advances in percutaneous coronary revascularisation therapy as described above, we might already have reached the stage that the theoretical advantages of complete revascularisation may overpass the disadvantages of the extended intervention aiming at complete revascularisation.

However adequate powered, large sized prospective randomised trials are required to investigate if :
a) complete revascularisation in STEMI patients will improve outcomes compared to culprit lesion revascularisation only, and
b) whether it should be performed during PPCI or in a staged procedure.

Another challenge for the interventional cardiologist in the decision making process regarding the need of revascularisation of the non-culprit artery is the discrepancy between the angiographic findings and the true physiologic evaluation of coronary artery stenosis[22].

While this discrepancy is true in the setting of stable coronary disease, in acute coronary syndromes and especially STEMI, which are often associated with a reduction of flow velocity not only in the culprit artery but also in the non culprit arteries, angiographic grading of the severity of the non-culprit stenosis becomes even more difficult[23].

## Fractional flow reserve

Fractional flow reserve[24,25] has evolved as the golden standard for the assessment of flow-limiting coronary obstructions in the cathlab. This technique uses the value of the ratio between the pressures, measured with the help of a pressure wire, respectively proximally and distally to the coronary obstruction site, during maximally induced hyperaemia, as a cut-off value to differentiate clinically relevant (significant) flow-limiting obstructions from clinically non relevant ones. The maximal FFR value is 1 and a FFR $\leq$ 0.80 indicates a flow limiting obstruction. Previous studies have shown that if revascularisation should occur it should address only flow-limiting coronary lesions as treatment of non-flow limiting lesions is associated with worse outcomes than optimal medical treatment[26] ref.
At the moment, we assume that treatment of flow-limiting lesions is better than optimal medical treatment, however this has not yet been directly shown in a prospective randomised trial. A recent study has shown that FFR-guided revascularisation in patients with multivessel disease presenting with stabilised coronary disease resulted in a significant reduction in the frequency of death or MI (11.1% vs. 7.3%; P=0.04) when compared to angiography guided revascularisation[27]. This approach resulted also in a strong trend towards less reinterventions for angina pectoris, while no differences were seen in quality of life. Furthermore, FFR guided approach strongly reduced treatment costs and duration of hospitalisation.

The actual guidelines have incorporated the role of FFR in the decision making process for revascularisation in stable coronary syndromes.

De Bruyne et al[28] have shown already that FFR can reliably assess the hemodynamic severity of non-culprit coronary artery stenosis during the acute phase of acute myocardial infarctions. Therefore, FFR may offer the same advantages in the decision making process on revascularisation of the non-culprit artery in patients presenting with STEMI, similarly as in stable coronary syndromes.

## Hypothesis

FFR-guided complete percutaneous revascularisation of all flow-limiting stenoses in the non-IRA performed within the same procedure or hospitalisation as the primary PCI will improve clinical outcomes compared to the staged revascularisation, guided by prove of ischemia or residual angina complaints, as recommended from the guidelines.

**Rationale for FFR-guided revascularisation during primary PCI for STEMI**

In the FFR-guided complete revascularisation group, FFR measurements will be used to guide the decision for percutaneous revascularisation in all non-IRA lesions that show an angiographic stenosis of 50% or more by quantitative coronary angiography (QCA) measurements or visual estimation in arteries and side branches of $\geq$ 2.0 mm in diameter. FFR should not be used to guide the decision for revascularization in the culprit artery as these measurement are not reliable during the acute phase of STEMI.

## Assumptions

We expect that similarly to stable coronary artery disease also during STEMI presentation, FFR measurements will accurately identify the flow-limiting lesions and therefore will reduce the need for revascularisation of non flow-limiting lesions that appear significantly stenosed on angiography, reducing in this way the periprocedural and long term complications that have been shown to arise from such a treatment.

On the other side the rationale of revascularisation of flow-limiting stenosis in non-IRA despite the absence of direct evidence from FFR trials relies on findings from nuclear studies where optimal medical treatment resulted in worse outcomes in death or myocardial infarctions when large areas of ischemic myocardium were involved compared to revascularisation[29]. This concept that FFR may better identify functionally significant stenosis and that FFR guided revascularization also has a better outcome than optimal medical management in patients with stable coronary artery disease has been shown to be true in the recent FAME II trial (de Bruyne et al. NEJM 2012;367:991-1001). Therefore, we would like to show that percutaneous revascularisation for flow-limiting lesions will result in better clinical outcomes compared to optimal medical treatment.

We also expect that FFR-guided complete revascularisation during the primary PCI or very shortly thereafter will result in better clinical outcomes compared to revascularisation during a staged procedure based on proven ischemia or symptoms of angina, often nowadays assessed after discharge of the primary event.

Furthermore FFR-guided complete revascularisation approach is expected to significantly reduce the treatment costs and hospitalisation duration as it probably will abolish non-invasive stress testing and re-admissions.

Therefore, we would like to perform a prospective randomised trial in patients with multivessel coronary disease presenting with STEMI that will prove the above mentioned hypothesis and each of the assumptions.

## Trial design

We will conduct an investigator initiated prospective randomised clinical trial in all-comer consecutive patients with multivessel coronary artery disease presenting with STEMI and amenable to treatment with primary PCI within < 12 h from the onset of symptoms.

## Study population

885 patients with multivessel coronary artery disease presenting with STEMI will be randomised in a 1:2 fashion in this study.

## Inclusion Criteria

All patients between 18-85 years presenting with STEMI who will be treated with primary PCI within 12 hours after the onset of symptoms* and have at least one stenosis of ≥50% in a non-IRA on QCA or visual estimation of baseline angiography and judged feasible for treatment with PCI by the operator.

*Patients with symptoms for more than 12 hours but ongoing angina complaints can be randomised.

## Exclusion Criteria

1. Left main stem disease (stenosis > 50%)
2. STEMI due to in-stent thrombosis
3. Chronic total occlusion of a non-IRA
4. Severe stenosis with TIMI flow ≤ II of the non-IRA artery.
5. Non-IRA stenosis not amenable for PCI treatment (operators decision)
6. Complicated IRA treatment, with one or more of the following;
    - Extravasation,
    - Permanent no re-flow after IRA treatment (TIMI flow 0-1),
    - Inability to implant a stent
7. Known severe cardiac valve dysfunction that will require surgery in the follow-up period.
8. Killip class III or IV already at presentation or at the completion of culprit lesion treatment.
9. Life expectancy of < 2 years.
10. Intolerance to Aspirin, Clopidogrel, Plasugrel, Ticagrelor, Heparin, Bivaluridin, or Everolimus and known true anaphylaxis to prior contrast media of bleeding diathesis or known coagulopathy.
11. Gastrointestinal or genitourinary bleeding within the prior 3 months,
12. Planned elective surgical procedure necessitating interruption of thienopyridines during the first 6 months post enrolment.
13. Patients who are actively participating in another drug or device investigational study, which have not completed the primary endpoint follow-up period.
14. Pregnancy or planning to become pregnant any time after enrolment into this study.
15. Inability to obtain informed consent.
16. Expected lost to follow-up.

## Informed consent

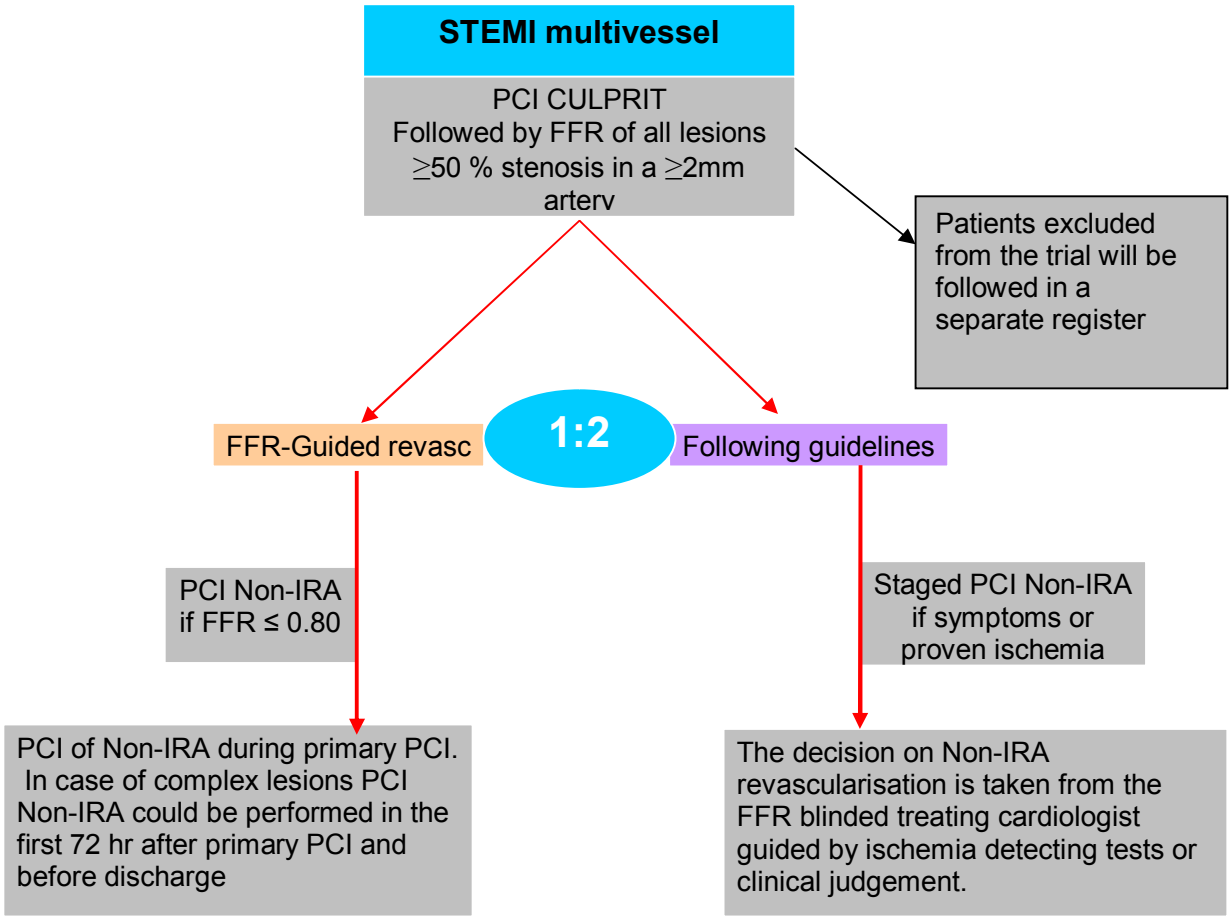
Informed consent will be obtained according to Good Clinical Practice guidelines prior to the procedure. Oral approval to participate in the trial in presence of a third independent (not involved in the study) person (cathlab or ambulance personnel) before the procedure followed by signature after the procedure is also accepted to avoid further delay of treatment.

## Randomisation

Randomisation will take place immediately after culprit vessel PCI . The randomisation will be delivered via closed envelopes. The envelopes will be stratified per centre and provided to the centres with blocks of 30 envelopes. Patients who fulfil the inclusion criteria but that for any reason will not participate in the trial will be followed in a separate register (only in Sweden centres and Maasstad hospital for 1 year, starting per 1 January 2013). These results will be extrapolated for the enrolment duration of the study).

Randomisation envelopes will be prepared by Gothia Forum.

## The trial design figure




Abbreviations: STEMI: ST-elevation myocardial infarction, PCI: Percutaneous coronary intervention, FFR: Fractional flow reserve, Non-IRA: Non infarct related artery.

# Trial design description

Patients will be enrolled and randomised in a 1:2 fashion between the FFR-guided revascularisation strategy, versus staged non-IRA revascularisation, as indicated from the actual guidelines, after completion of a successful culprit lesion PCI. All patients who present at least one lesion with a stenosis of approximately 50% or more in a non-IRA with a diameter of ≥ 2.0 mm and fulfil the inclusion and exclusion criteria will be enrolled.

All patients will receive a FFR measurement in all stenosis of approximately 50% or more in a non-IRA with a diameter of ≥ 2.0 mm

In the FFR-guided complete revascularisaton strategy group all flow limiting (FFR≤0.80) lesions will receive treatment by PCI and stenting. The non-IRA PCI should be performed during the same intervention. Exceptions can be made for complex lesions where the operator estimates that the revascularisation procedure will require significant contrast overload which may lead to deterioration of cardiac and renal function of the patient. Such procedures can be performed in a second procedure which should take place within the same hospitalisation, preferably within 72 hours.
All lesions with a FFR measurement of >0.80 will not be treated.

In the randomised to guidelines group the procedure will stop after the FFR measurements and the patient will be referred to his treating cardiologist who will decide whether a staged PCI of the non-IRA artery should take place. The treating cardiologist will be blinded for the FFR measurements (but not angiographic imaging) and must make a decision based on conventional non-invasive ischemia detecting tests or clinical signs and symptoms i.e. very typical angina symptoms in patients with angiographic significant stenosis. After the PPCI procedure the FFR values will not be reported in the conventional PCI report but will be registered in the study database only. If the treating cardiologist decides to perform the non-IRA PCI revascularisation, than such treatment should take place within six weeks (45) days from the primary PCI in order to count as a scheduled staged PCI procedure. Any other revascularizations of any lesions after these 6 weeks are identified as unscheduled and therefore counted as an event. Per definition the treating cardiologist should be a different person from the operator.

All revascularisations procedures will be defined as clinically indicated or not.clinically indicated by the independent clinical event committee. Non clinically indicated revascularisation will be counted as an event.

Blinding for the FFR results is required to perfectly mimic the standard care treatment in the randomised to guidelines group and avoid bias in further decision tree.
Blinding for the FRR results in this group allows for the following subgroup (shown in figure 2) comparisons and will try to give answers to following dilemmas in the treatment of STEMI patients presenting with multivessel disease:

1) Clinical outcomes differences between PCI treatment vs optimal medical treatment in patients with at least one FFR positive lesion ( group c vs group d)
2) Staged PCI versus acute (during PPCI) revascularistion of FFR positive lesions (group a vs group c)
3) Optical Medical Treatment versus PCI treatment of FFR negative lesions (group b + f vs group e)

In order to balance the number of patients in these subgroups we chose for a 1:2 randomisation pattern.

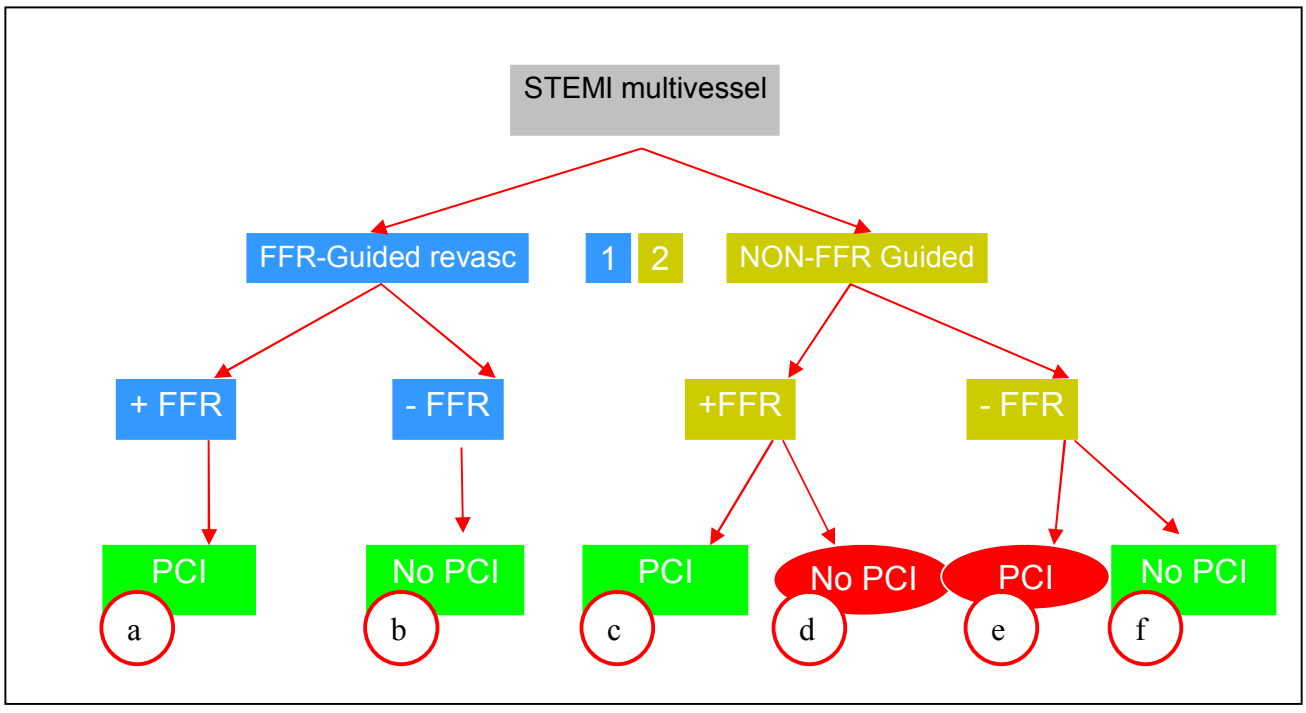



Figure 2: Subgroups resulting from this randomisation.

# Endpoints

## Primary endpoint:

Composite endpoint of all cause mortality non-fatal Myocardial Infarction, any Revascularisation and Cerebrovascular Events (MACCE) at 12 months between groups ( a+b versus c-f).

## Secondary endpoints:

1. Primary endpoint at 24 and 36 months as well as outcomes of each component of the primary endpoint at 12, 24 and 36 months.

2. Primary endpoint rates at 12, 24 and 36 months in the subgroup of patients receiving staged or acute PCI treatment for FFR positive lesions in the non-IRA vs the subgroup of patients with FFR positive lesion that received optimal medical treatment. {figure 2, subgroups (**a+c**) vs subgroup **d**}

3. Primary endpoint rates at 12, 24 and 36 months in the subgroup of patients receiving acute PCI treatment for FFR positive lesions in the non-IRA vs the subgroup of patients receiving staged PCI treatment for FFR positive lesions in the non-IRA (figure 2 subgroups **a** vs **c**)

4. Primary endpoint rates at 12, 24 and 36 months in the subgroup of patients receiving staged PCI treatment for FFR negative lesions in the non-IRA vs the subgroup of patients not receiving PCI treatment for FFR negative lesions in the non-IRA. ( figure 2 subgroups **e** vs **b**+ **f**)

5. Composite endpoint of Cardiac death, Myocardial Infarction, any Revascularisation, Stroke and Major bleeding at 12, 24 and 36 months (NACE i.e. Net Adverse Clinical Events)

6. A composite of hospitalisation for heart failure and unstable angina pectoris at 12, 24, and 36 months

7. All cause mortality or Myocardial infarction at 12, 24 and 36 months

8. Any revascularisation at 12, 24 and 36 months

9. Stent thrombosis at 12 months, 24 and 36 months

10. Bleeding at 48 hr and 12 months.

11. Treatment costs 12 months, 24 and 36 months

## Definitions

### Death

All deaths are considered cardiac unless an unequivocal non-cardiac cause can be established. Specifically, any unexpected death even in patients with coexisting potentially fatal non-cardiac disease (e.g. cancer, infection) should be classified as cardiac.

### Cardiac death

Any death due to immediate cardiac cause (e.g. MI, low-output failure, fatal arrhythmia). Unwitnessed death and death of unknown cause will be classified as cardiac death. This includes all procedure related cardio-vascular deaths including those related to concomitant treatment.

### Non-cardiac death

Any death not covered by the above definitions, including death due to infection, sepsis, pulmonary causes, accident, malignancy, suicide or trauma.

### Myocardial infarction

All myocardial infarction data will be analyzed according the ARC definitions[30] and per historical protocol definitions. Both ARC and historical definitions will be used for the primary and secondary endpoints. Currently the ARC MI definition is open for discussion in the community. Therefore we have powered the trial for both historical and ARC definitions.

**ARC MI definitions**

| Classification | Biomarker Criteria | Additional Criteria |
|---|---|---|
| Peri-procedural PCI | Troponine > 3 times UNL or<br>CK-MB ≥ 3 times UNL | Baseline value < UNL |
| Peri-procedural CABG | Troponine > 5 times UNL or<br>CK-MB > 5 times UNL | Baseline value < UNL **AND**<br>Any of the following:<br>• New pathologic Q waves or LBBT<br>• New native or graft vessel occlusion<br>• Imaging evidence of loss of viable myocardium |
| Spontaneous | Troponine > UNL or<br>CK-MB > UNL | |
| Sudden death | Death before biomarkers obtained or before expected to be elevated | Symptoms suggestive of ischemia **AND**<br>Any of the following:<br>• New ST elevation or LBBT<br>• Documented thrombus by angiography or autopsy |
| Re-infarction | Stable or decreasing values on 2 samples AND 20% increase 3-6 hours after second sample | If biomarkers increasing or peak not reached then insufficient data to diagnose recurrent MI |

**Protocol MI definitions**

**Peri-procedural during PCI (within 48 hours after PCI)**

An rise of CKMB >3 times ULN is considered evidence of peri-procedural MI.

**Periprocedural MI during CABG (within 7 days after CABG)**

In patients undergoing coronary artery bypass surgery during the study follow-up period, a peri-procedural MI is diagnosed by a rise in the CK-MB level of five times the upper limit of normal

**Peri-procedural Myocardial Infarction in the setting of evolving MI:**

1) If the peak total CK (or CK-MB) from the index infarction has not yet been reached: recurrent chest pain lasting >20 minutes (or new ECG changes consistent with MI) AND the peak CK (or CK-MB in absence of CK) level measured within 24 hours after the event is elevated by at least 50% above the previous level.
2) If the elevated CK (or CK-MB) levels from the index infarction are falling or have returned to normal within 24 hours post index PCI: EITHER a new elevation of CK >2 x ULN within 24 hours post index PCI if the CK level has returned to <ULN OR a rise by >50% above the previous nadir level if the CK level has not returned to <ULN.

**Spontaneous MI (adapted from ESC/ACC guidelines EHJ 2000 and JACC2000)**

Either one of the following criteria satisfies the diagnosis for an acute, evolving or recent MI:

1) Typical rise and gradual fall (Troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following:
    a) ischemic symptoms;
    b) development of pathologic Q waves on the ECG

c) ECG changes indicative of ischemia (ST segment elevation or depression);

2) Pathologic findings of an acute MI.

**Q-wave MI**

Development of new pathological Q waves in 2 or more contiguous leads with or without post-procedure CK or CK-MB levels elevated above normal.

**Non-Q wave MI**: Confirmed MIs (see above) without the development of Q-Wave

## Revascularisation

This trial compares two revascularisation strategies, therefore any revascularisation procedure (PCI or CABG) not foreseen in the trial design specified revascularisation strategy will be considered as an event as it shows failure of the strategy.

More specifically, in the FFR guided group most of the revascularisation will occur during the primary PCI. However, in complex lesions revascularisation of non-IRA can be staged but within the same hospitalisation. These interventions, called **delayed non-IRA revascularisations** are specified in the end of the primary PCI and therefore will not count as an event. All reinterventions that do not qualify as **delayed non-IRA revascularisations** will be counted as an event.

In the guideline guided group the staged non-IRA revascularisations can take place until day 45 post primary PCI. These will be called **staged non-IRA revascularisations** and will not be counted as an event revascularisation, unless the Clinical Event Committee considers these revascularisations as clinically not justifiable.

All urgent revascularisations (in both strategy arms) will be counted as events. All other revascularisations that do not qualify as **delayed** or **staged non-IRA revascularisations** will be counted as events. All revascularisations that will take place beyond the 45 days will also be counted as event revascularisations.

**Clinically indicated:**

A revascularization is clinically indicated if angiography shows a percent diameter stenosis ≥50% (QCA) **and** if one of the following occurs:

1) A positive history of recurrent angina pectoris presumably related to the target vessel.
2) Objective signs of ischemia at rest (ECG changes) or during exercise test (or equivalent) presumably related to the target vessel.
3) Abnormal results of any invasive functional diagnostic test (e.g. Doppler flow velocity reserve, fractional flow reserve). The results of the test must be documented in the Case Report Form.

**Not Clinically indicated are re-interventions for**:

1. all stenoses in absence of ischemic signs or symptoms.

## Stent Thrombosis

We follow the ARC definitions[30]. Stent Thrombosis should be reported as a cumulative value at the different time points and with the different separate time points. Time 0 is defined as the time point after the guiding catheter has been removed and the patient left the Cathlab.

**Timing**

| | |
|---|---|
| Acute stent thrombosis(*): | 0 – 24 hours post stent implantation |
| Subacute stent thrombosis(*): | >24 hours – 30 days post stent implantation |
| Late stent thrombosis: | >30 days – 1 year post stent implantation |
| Very late stent thrombosis: | >1 year post stent implantation |

(*) acute/subacute can also be replaced by early stent thrombosis. Early stent thrombosis (0 – 30 days) – this definition is currently used in the community.

We recognize three categories of evidence in defining stent thrombosis:

1) Definite
2) Probable
3) Possible

**1) Definite* stent thrombosis**

**Angiographic confirmation of stent thrombosis†**

The presence of a thrombus that originates in the stent or in the segment 5 mm proximal or distal to the stent and presence of at least 1 of the following criteria within a 48-hour time window:

- Acute onset of ischemic symptoms at rest
- New ischemic ECG changes that suggest acute ischemia
- Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous MI)

*Nonocclusive thrombus*

Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis)

seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream.

** Definite stent thrombosis is considered to have occurred by either angiographic or pathological confirmation.*

*†The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis (silent occlusion)*

*Occlusive thrombus*

TIMI 0 or TIMI 1 intra stent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originates from the side branch).

*Pathologic confirmation of stent thrombosis:*

Evidence of recent thrombus within the stent determined at autopsy

**2) Probable stent thromosis**

Clinical definition of probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases:

1) Any unexplained death within the first 30 days.

2) Irrespective of the time after the index procedure any myocardial infarction (MI), which is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause.

**3) Possible stent thrombosis**

Clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death following intracoronary stenting until the end of the follow-up period.

**Stroke**

Acute neurological event of at least 24 hours of duration, with focal signs and symptoms and without evidence supporting any alternative explanation. Diagnosis of stroke requires confirmation by cCT or MRI or pathological confirmation.

Ethiology:

*Hemorrhagic stroke:* including intraparenchymal, subarachnoid hemorrhage and subdural hematomas)

*Ischemic stroke*

*Unknown cause*: in which case there was no brain imaging or autopsy

Degree of severity:

*Non disabling stroke:*

if he or she had no sequels or only a minor deficit (with the functional status unchanged). Modified Rankin scale grade of < 3 (see below)

*Disabling stroke:*

if at the time of hospital discharge he or she had a moderate deficit (substantial limitation of activity and capabilities) or a severe deficit (inability to live independently or work). Modified Rankin scale grade of > 4 (see below)

*Modified Rankin Scale - Stroke severity assessment scale*

Scale 0

No symptoms at all

Scale 1

No significant disability despite symptoms: able to carry out all usual duties and activities

Scale 2

Slight disability: unable to carry out all previous activities but able to look after own affairs without assistance

Scale 3

Moderate disability: requiring some help, but able to walk without assistance

Scale 4

Moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance

Scale 5

Severe disability: bedridden incontinent and requiring constant nursing care and attention

## Urgent Revascularisation

Any PCI or bypass surgery for recurrent ischemia that in the investigators opinion can not be delayed for more than 24 hours and is defined by the investigator as a non-elective procedure.

## Target Lesion revascularisation

TLR is defined as any ischemia-driven repeat PCI of the target lesion or bypass surgery of the target vessel. Target lesion is defined as the vessel segment composed by the treated segment including the adjacent 5mm distal and proximal to the treated segment.

## Target Vessel revascularisation

TVR as any ischemia-driven repeat PCI or bypass surgery in any lesion of the target vessel. The target vessel is one of the 3 main epicardial coronary artery or bypass graft that contains the target lesion.

## NYHA Classification of Heart Failure

*Class I*

No limitation of activities; patients suffer no symptoms from ordinary activities.

*Class II*

Slight, mild limitation of activity; patients are comfortable with rest or with mild exertion.

*Class III*

Marked limitation of activity; patients are comfortable only at rest.

*Class IV*

Patients who should be at complete rest, confined to bed or chair; any physical activity brings on

## Killip Classification of Heart Failure

*Class I*

The absence of rales over the lung fields and the absence of an S3.

*Class II*

The presence of rales, that do not clear with coughing, over one half or less of the lung fields or the presence of an S3.

*Class III*

The presence of rales that do not clear with coughing, over more than half the lung fields.

*Class IV*

Cardiogenic shock

## Cardiogenic Shock

Must fulfil one of the following criteria:

1. Systolic blood pressure < 90 mmHg for at least 30 minutes

    OR

    The need for supportive measures to maintain a systolic blood pressure > 90 mmHg

    AND

    End-organ hypo-perfusion (cool extremities or urine output < 30 ml/h and a heart beat > 60 bpm)

OR

2. Cardiac Index <2.2 l/min per square meter body surface area

    AND

    a pulmonary capillary wedge pressure of at least 15 mmHg

    AND

End-organ hypo-perfusion (cool extremities or urine output < 30 ml/h and a heart beat > 60 bpm)

## Major bleeding definitions

Multiple clinical and laboratory definitions of bleeding will be used for full assessment of the risk of bleeding. These definitions will be based on criteria from the Global Utilization of Streptokinase

and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial[31] (mild, moderate, or severe or life-threatening bleeding on the basis of use or non use of transfusions and the presence or absence of hemodynamic compromise), the Thrombolysis in Myocardial Infarction (TIMI) trial[32] (minor or major bleeding on the basis of clinical and laboratory findings), and the Acute Catheterization and Urgent Intervention Triage Strategy trial (ACUITY; NCT00093158)[33] (major bleeding on the basis of detailed clinical assessment, changes in the hemoglobin level, hematomas >5 cm, and the need for blood transfusion).

**For the bleeding secondary endpoint the TIMI (major and minor) criteria will be used** ,
However for further descriptive value the criteria for Acuity and GUSTO will also be captured in the database.

***Detailed description of bleeding following different trials***

**GUSTO**

**Severe or Life Threatening**

Either intracranial haemorrhage or bleeding that causes hemodynamic compromise and requires intervention

**Moderate**

Bleeding that requires blood transfusion but does not result in hemodynamic compromise

**Mild**

Bleeding that does not meet the criteria for severe or moderate

**TIMI**

**Types of TIMI Bleeding**

**1. Major**

Any intracranial bleeding

OR

Clinically overt signs of hemorrhage associated with a drop in hemoglobin (Hgb) of ≥ 5 g/dL or an absolute drop in hematocrit of at least 15% (when Hgb not available) .

**2. Minor**

Any clinically overt signs of hemorrhage (including imaging) that is associated with a fall in Hgb of 3 to < 5 g/dL (when a Hgb value was not available, a fall in the hematocrit of 9 % to <15% points) if no bleeding site was identifiable, or drop of ≥40 g/L in hemoglobin (or ≥12% in hematocrit)

**3. Medical Attention:**

Any overt sign of hemorrhage that requires medical evaluation, medical treatment (including discontinuation of medications), or surgical treatment, and that does not meet criteria for a major or minor bleeding event, as defined above.

**4. Minimal**

Any overt bleeding event that does not meet the criteria above

**Relationship of Bleeding to Death**

**1. Fatal Bleeding**

Death in which a bleeding event directly led to death within 7 days. Examples of fatal bleeding events are an intracranial hemorrhage that led to herniation of the brain and death within 24 hours, and a massive gastrointestinal hemorrhage that results in shock, hemodynamic collapse, and death. If a bleeding event is considered fatal, then the cause of death must be either intracranial or non-intracranial bleeding.

**2. Bleeding Contributed to Death**

Death in which a bleeding event was part of a causal chain of medical events that ultimately led to death within 30 days of the bleed, but bleeding was not directly and/or immediately related to the subject's death. An example of bleeding contributing to death is a large retroperitoneal bleed that leads to surgical evacuation, development of a subsequent abscess in the area of bleeding that leads to sepsis, multiorgan failure, and death 10 days after the onset of bleeding. If bleeding has contributed to death (but the bleeding was not categorized as "fatal"), then the cause of death must be recorded as something other than intracranial / non-intracranial bleeding.

**c. Bleeding in the Setting of Coronary Artery Bypass Graft Surgery (CABG)**

Minor and minimal bleeding are not adjudicated in the setting of CABG.

As a drop in hemoglobin and transfusions are commonplace in routine CABG cases, one of the following criteria must be met to qualify for major bleeding in any of the preceding definitions:

1. Fatal bleeding (i.e., bleeding that directly results in death)
2. Perioperative intracranial bleeding
3. Reoperation following closure of the sternotomy incision for the purpose of controlling bleeding
4. Transfusion of ≥ 5 units of packed red blood cells (PRBCs) or whole blood within a 48 hour period. Cell saver transfusion will not be counted in calculations of blood products
5. Chest tube output > 2 L within a 24 hour period

**ACUITY**

**Major Bleeding is defined as**

1. Intracranial bleeding
2. Intraocular bleeding
3. Access site hemorrhage requiring intervention
4. ≥ 5 cm diameter hematoma
5. Reduction in hemoglobin concentration of ≥ 4 g/dL without an overt source of bleeding
6. Reduction in hemoglobin concentration of ≥ 3 g/dL with an overt source of bleeding
7. Reoperation for bleeding
8. Use of any blood product transfusion

**Minor bleeding**

Clinically overt bleeding that did not meet criteria for major bleeding.

**Smoking Status**

*Smoker:* regular cigarette smoking in the prior 6 months

*Nonsmoker:* no regularly cigarettes smoking at any time (according to WHO also former smoker that quit smoking for at least 10 years).

*Former smoker:* those who had quit smoking at least 6 months before the index PCI.

**Diabetes Mellitus**

Active treatment with insulin or an oral hypoglycemic agent on admission. In patients diagnosed with diabetes who are on dietary therapy alone, documentation of an abnormal fasting blood glucose (>125 mg/dl), blood glucose >200mg/dl at any time, or abnormal glucose tolerance test based on the World Health Organization criteria is required.

**Family History of Premature CAD**

Myocardial infarction, angiographic documentation of CAD or sudden abrupt death without obvious cause, before the age of 55 in a first-degree blood male relative (parent, sibling, or children related by blood) or before the age of 65 in a first-degree blood female relative.

**History of Hypercholesterolemia**

Patients with any one of the following:
1. Prior total cholesterol > 200 mg/dl
2. Prior treatment with a lipid lowering agent

**Arterial Hypertension**

Arterial hypertension is considered to be present when a person's systolic blood pressure is 140 mmHg or greater, and/or their diastolic blood pressure is 90 mmHg or greater on 2 different occasions, or active treatment with antihypertensive drugs.

**Multivessel Disease**

Presence of angiographically significant lesions (>50% lumen narrowing) in ≥2 major epicardial coronary arteries.

**Renal failure**

A creatinine value of more than 133 µmol/l or patients in dialysis.

# Statistical Considerations

Compare Acute is a prospective, multicenter, randomized trial aiming to compare a new strategy in treatment of STEMI in patients with multivessel disease compared to the actual standard of care in respect to the primary endpoint of cardiac death, non fatal myocardial infarction and any revascularization at 12 months.

The event rates for both groups were defined as follows:
In the FFR guided group the event rates were estimated based on data from the COMPARE trial STEMI subgroup analysis where the rates of all death, myocardial infarction, and target lesion revascularisation in the Xience V arm was found to be 6.7 %. Multivessel treatment in the Xience V group occurred at the same frequency as expected in the FFR guided group therefore we estimate a primary endpoint of 7%. Counting a rate of 1% for stroke a primary endpoint rate of 8% is expected.

In the staged, guideline guided group estimations were based on the following assumptions, which represent the combined experience of all participating centres:

a) 60% of patients will receive a exercise stress test (sensitivity 67%, specificity 70%)[34]

b) 20% will receive a nuclear scan (sensitivity 81%, specificity 85-95%) [34]

c) 20 % will receive no ischemia detecting test but will be guided by clinical symptoms and angiographic data.

Decision *to revascularisation* will be taken in 70% of patients with positive FFR. Decision to *not perform revascularisation* will be taken in 50% of patients with negative FFR.

Based on the results of the FAME angiographic analysis[35] and taking in account that a lesion of > 50% DS will have an equal distribution of FFR negative and positive patients in the staged, guideline guided group.

An event rate of 20 % (mainly due to unplanned revascularisations) on top of standard STEMI treatment event rates is expected for FFR+ non-IRA patients that will receive optical medical treatment only.

Higher event rates are expected also for all patients treated in a staged setting due to periprocedural complications.
Stroke rates of 1.0% are expected in the FFR group and 1.5% (50% more procedures) are expected in the non-FFR guided group.

Based on these assumptions and data, an event rate of 14.5% is expected in the staged, guideline guided non-IRA revascularisation group.

A total sample size of 858 patients (286 in the FFR-guided group, 572 in the control group) is sufficient to obtain a power of at least 80% with a two-sided false positive error rate (alpha) of 5% for rejecting the null-hypothesis of no difference when the endpoint incidence is 8% in the FFR guided group vs 14.5% in the control group, using the Pearson Chi-square test for two proportions assuming an asymptotic normal distribution with a normal approximation method.

Considering a 3% loss in follow-up a total of 885 (295/590) patients will be randomised in this trial. Categorical variables will be assessed with the use of $\chi^2$ or Fisher's exact tests, whereas continuous variables will be assed with the Wilcoxon rank-sum test.

The results in both groups for the primary endpoint as well as for the secondary endpoints will be presented as time to event curves (Kaplan-Meyer).

# Trial Conduct

## Cathlab procedure

The primary PCI will be performed within 12 hr after onset of symptoms, however patients with symptoms for more than 12 hr and ongoing ischemia can also be randomised.

Standard care cathlab techniques and equipment will be used to perform the coronary angiography imaging and primary PCI. Artery puncture site is left at the discretion of the operator, although radial approach is strongly recommended to avoid bleeding complications at the puncture site. A diagram or description of the coronary artery tree will be completed at the end of the procedure to indicate which segments have lesions with approximately 50% or more diameter stenosis. If the lesion extends over more than one segment the most proximal segment should be stated.

Assessment of left ventricle function or wall motion abnormalities are at the discretion of local practice.

Thrombosuction and pre-dilation of the lesion are left at the discretion of operator.

Intracoronary injection of nitrates followed by two orthogonal projections for culprit lesion evaluation and stent size choice are strongly recommended.

Stenting should by protocol be performed. Everolimus Eluting Xience V/ Prime /Expedition should be used in this study as these are at the moment the most safe drug-eluting stents clinically proven in this setting.

Post-dilation will be left at the discretion of the operator.

After primary PCI, enrolled patients are randomized. FFR measurements will be performed after the randomisation. To guarantee for uniformity of these measurements the RADI (St Jude) FFR system is strongly recommended..

Measurements of ACT before the FFR procedure is recommended.

The protocol for FFR measurement is shown in appendix 1

For the PCI of the non-IRA the same recommendations as for the PCI of the culprit lesion are valid.

**Anticoagulant and antithrombotic treatment**

Bivaluridin is the anticoagulant of choice in this trial. For dosage see Appendix 2. Previous Heparin administration (eventually during transport in the ambulance) is not a contraindication.

All patients should receive a loading dose of aspirin of 150–300 mg per os or 250 (–500) mg bolus i.v., followed by 75–100 mg daily lifelong.

Prasugrel or Ticagrelor are the P2Y12 inhibitors of choice in treatment of STEMI conform the latest guidelines, therefore we strongly recommend their use in this study. Patients who have received a loading dose of Clopidogrel may receive prior to stenting a loading dose of Prasugrel or Ticagrelor respectively 60 mg and 180mg followed by 10 mg once daily for the prasugrel or 90 mg twice daily for the Ticagrelor in the first 12 months after the last procedure.

The use of IIbIIIa inhibitors is not recommended but can be used as bailout.

# Trial Sites

The trial will be performed in big-volume interventional cardiology centres in Europe and Asia.

Other centres in other countries can join in a second timing if needed.

**Sites in the Netherlands:**

Leading centre:

Maasstad Hospital Rotterdam

Haga Hospital Den Haag

Academisch Medisch Centrum (AMC) Amsterdam

**Sites in Sweden:**

Gotheborg University Hospital

**Sites in Germany**:

Herzzentrum Segeberger Kliniken, Bad Segeberg

University Hospital Rostock, Rostock

Herzzentrum Bad Krozingen, Bad Krozingen

Deutsches Hertzzentrum, München

Klinikum Ingolstadt, Ingolstadt

Klinikum Links der Weser, Bremen

**Sites in Luxembourg**:

Centre Hospitalier de Luxembourg

**Sites in Norway**:

Rigshospitalet University of Oslo

**Sites in Singapore:**

Tan Tock Seng Hospital

Khoo Teck Puat Hospital

**Sites in Poland**

**Sites in Czech Republic**

# Trial management

The trial will be performed under supervision of the Steering Committee.
For ethical and safety reasons, three formal interim analyses will be performed when 25%, 50% and 75% of the suspected number of primary endpoint events in patients allocated to FFR guided revascularisation group or the actual standard of care group have occurred (i.e. after 32, 63 and 95 events, respectively). The independent Data Safety Monitoring Board (DSMB) will review these analyses and inform the Steering Committee. The DSMB will consider the primary endpoint and secondary endpoints consistency, and the consistency of treatment effects across clinically relevant subgroups.

The DSMB will also monitor the study to evaluate if each of the two groups is associated with increased mortality. For these safety analyses, premature termination of the trial should be considered.

The DSMB will consist of 3 members.

First 5 patients in all centres will be fully monitored for all variables.
This will be followed by spot monitoring aiming at a site monitoring for a total of 25% of trial population for 100% of variables and for the rest of the population for 20% of the variables.

Event collection will be done by patients contacts or monitoring of patient charts up to 1 year at 30 and 360 days. Thereafter, event collection will be done by correspondence or telephone contact with all patients at 2 and 3 years. In parallel to this, information from national health registers in respective countries will be used.

Events will be analysed by an independent CRO and will be adjudicated by an independent Clinical Evaluation Committee (CEC).

All sites will undergo training prior to study initiation. Training will cover how to obtain informed consent, randomisation, data entry, the catheter laboratory procedure for guide wire based coronary pressure measurement, and how to complete the electronic case record. Training could be delivered either by a Site Visit or through a single meeting attended by PIs and support staff from all of the sites.

## Study duration

The study is expected to finish enrolment in 3.5 years (+/- 2) months from the start date.

We aim to produce the first manuscript (30 day results) at 45 (+/-1) months after the start of the study. The main manuscript is expected at 55 (+/-1) months after the start of the study.

## Regulatory approvals

This clinical investigation will test a strategy guided by a diagnostic device. We do not propose a trial of a medicinal product or therapeutic device. The Pressure Wire (RADI/St. Jude Medical) is CE marked as a diagnostic medical device and our proposal is to use this device in line with its existing purpose.

An approval for local and national ethical committees will be sought in all participating centres and countries.

The clinical trial does not involve a medicinal product and is therefore not subject to The European Clinical Trials Directive 2001/20/EC.

Multicentre research ethics approval would be sought and obtained. The clinical trial will be subject to the Good Clinical Practice Directive (Directive 2005/28/EC).

The trial is registered at ClinicalTrials.gov: NCT01399736

## Sponsor

MCR B.V., Maasstadweg 21, 3079 DZ Rotterdam, the Netherlands.

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# Appendix 1 FFR protocol

**Adenosine during FFR I.C. administration**

**Drug Group**
Anti-arrhythmia

**Working**
Adenosine is a molecule produced from the human body. It increases the blood flow in the coronary arteries by 200 to 400%. It temporarily blocks the AV node. Further it is a vasodilatator. The half-life is a maximum of 30 seconds.

**Indications**
- FFR-measurement

**Contra-indications**
- Bronchospasm
- Hypotension
- SSS and AV-block (2-3)

**Side Effects**
- AV block
- Flushing
- Angina
- Dyspnoe
- Atrial en ventricular arythmias
- HR increases between 15 and 25%
- Drop in blood pressure up to 6%

**Antidote**
Theophylline

**Dose**
Bolus for the RCA: start with 40 mcg, and increase stepwise till max. 100 mcg till no further drop in FFR is obtained.
Bolus for the LCA: start with 60 mcg ,and increase stepwise till max. 100 mcg till no further drop in FFR is obtained.

*Step 1*
Flacon of Adenosine 500 mg in 100 ml = 5 mg/ml
2 ml (= 10 mg) diluted with NaCl 0,9% to 10 ml
10 mg in 10 ml = 1 mg/ml

*Step 2*
Take 1 ml diluted with NaCl 0,9% to 10 ml
1 mg in 10 ml = 0,1 mg/ml (= 100 mcg/ml)

*Step 3*
100 mcg = 1 ml given to the sterile personel,
who adds to this NaCl 0,9% to 10 ml
100 mcg in 10 ml = 10 mcg/ml

**Final Delivery Form**
Flacon 100 ml = 500 mg

**Extra Attention**
- Stop Persantin one day before use
- Inform the patient about possible side effects
- Maximum effect time, 30 to 90 seconds.
- Time for returning to normal ECG 30 to 120 seconds.

**Adenosine bij FFR I.V. administration**

**Drug Group**
Anti-arrhythmia

**Working**
Adenosine is a molecule produced from the human body. It increases the blood flow in the coronary arteries by 200 to 400%. It temporarily blocks the AV node. Further it is a vasodilatator. The half-life is a maximum of 30 seconds.

**Indications**
- FFR-measurement

**Contra-indications**
- Bronchospasm
- Hypotension
- SSS and AV-block (2-3)

**Side Effects**
- AV geleidingsstoornis
- Flushing
- Angina
- Dyspnoe
- Atrial en ventricular arythmias
- HR increases between 15 and 25%
- Drop in blood pressure up to 6%

**Antidote**
Theophylline

**Dose,** *see doseing schedule*
Mix 400cc NaCl with 500 mg Adenosine
Soloution: 1 mg/cc

**Packaging**
Flacon 100 ml = 500 mg

**Extra Attention**

- Administer via a centraal venous sheath.
- Stop Persantin one day before use
- Inform the patient about possible side effects
- Maximum effect time, 30 to 90 seconds.
- Time for returning to normal ECG 30 to 120 seconds.

**Dosing Schedule Adenosine during FFR I.V.**

Dose 140 mcg/kg/min
Infusion 1-999 cc/uur (OPTIMA PT)

| Weight | mcg/min | cc/min | Infusion Rate cc/uur |
|---|---|---|---|
| 50 | 7000 | 7 | **420** |
| 52.5 | 7350 | 7.35 | **441** |
| 55 | 7700 | 7.7 | **462** |
| 57.5 | 8050 | 8.05 | **483** |
| 60 | 8400 | 8.4 | **504** |
| 62.5 | 8750 | 8.75 | **525** |
| 65 | 9100 | 9.1 | **546** |
| 67.5 | 9450 | 9.45 | **567** |
| 70 | 9800 | 9.8 | **588** |
| 72.5 | 10150 | 10.15 | **609** |
| 75 | 10500 | 10.5 | **630** |
| 77.5 | 10850 | 10.85 | **651** |
| 80 | 11200 | 11.2 | **672** |
| 82.5 | 11550 | 11.55 | **693** |
| 85 | 11900 | 11.9 | **714** |
| 87.5 | 12250 | 12.25 | **735** |
| 90 | 12600 | 12.6 | **756** |
| 92.5 | 12950 | 12.95 | **777** |
| 95 | 13300 | 13.3 | **798** |
| 97.5 | 13650 | 13.65 | **819** |
| 100 | 14000 | 14 | **840** |
| 102.5 | 14350 | 14.35 | **861** |
| 105 | 14700 | 14.7 | **882** |
| 107.5 | 15050 | 15.05 | **903** |
| 110 | 15400 | 15.4 | **924** |
| 112.5 | 15750 | 15.75 | **945** |
| 115 | 16100 | 16.1 | **966** |
| 117.5 | 16450 | 16.45 | **987** |
| 120 | 16800 | 16.8 | **1008** |

# Appendix 2 Angiox /bivaluridine dosis in function of body weight

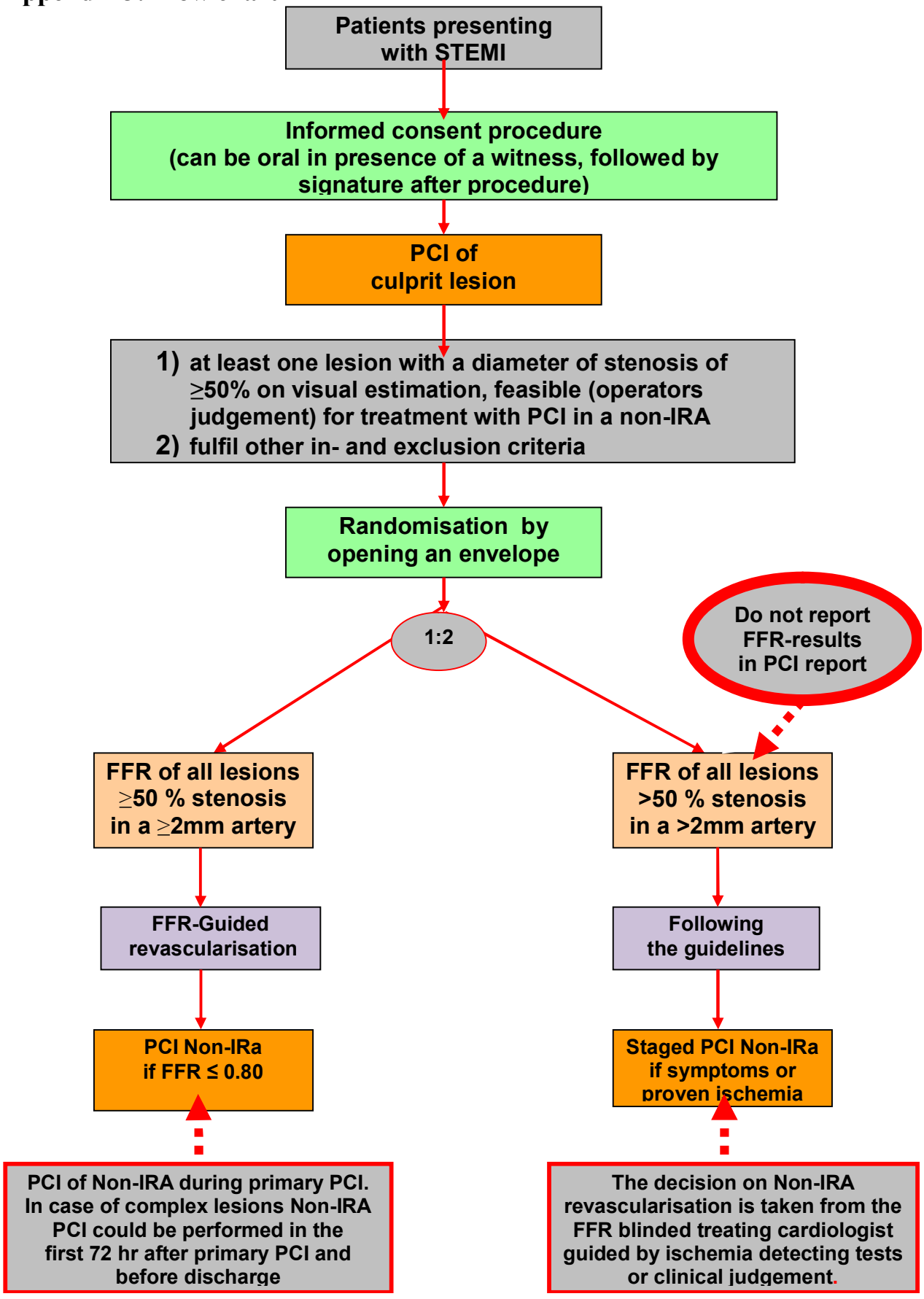
**Percutaneous Coronary Intervention (PCI)/Primary PCI in ST-segment Elevation Myocardial Infarction (STEMI) Patients**

**ANGIOX naive patients arriving directly to the catheterisation laboratory**

An initial intravenous (IV) bolus of 0.75 mg/kg of body weight followed immediately by an IV infusion of 1.75 mg/kg/h for at least the duration of the PCI procedure. The infusion may be continued for up to 4 hours post-procedure as clinically necessary.

| | | Patient weight (kg) | 43–47 | 48–52 | 53–57 | 58–62 | 63–67 | 68–72 | 73–77 | 78–82 | 83–87 | 88–92 | 93–97 | 98–102 | 103–107 | 108–112 | 113–117 | 118–122 | 123–127 | 128–132 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 5 mg/mL concentration | Bolus | (0.75 mg/kg) mL | 7 | 7.5 | 8 | 9 | 10 | 10.5 | 11 | 12 | 13 | 13.5 | 14 | 15 | 16 | 16.5 | 17 | 18 | 19 | 19.5 |
| | Infusion dose | (1.75 mg/kg/h) mL/h | 16 | 17.5 | 19 | 21 | 23 | 24.5 | 26 | 28 | 30 | 31.5 | 33 | 35 | 37 | 38.5 | 40 | 42 | 44 | 45.5 |
| | Infusion dose for renally impaired patients | (1.4 mg/kg/h) mL/h | 12.5 | 14 | 15.5 | 17 | 18 | 19.5 | 21 | 22.5 | 24 | 25 | 26.5 | 28 | 29.5 | 31 | 32 | 33.5 | 35 | 36.5 |

## Appendix 3: Flow chart



## Appendix 4: Coronary Anatomy - American Heart Association