Coronary microvascular dysfunction assessed by pressure-wire and CMR after STEMI is associated with long-term outcomes

Running title: Long-term prognostic value of MVO and high IMR in STEMI

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ABSTRACT

Objectives. We sought to evaluate the long-term prognostic implications of coronary microvascular dysfunction (CMD) when assessed with both cardiovascular magnetic resonance (CMR) and index of microcirculatory resistance (IMR) in patients with ST-elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PPCI).
Background. Post-ischaemic CMD can be assessed using the pressure-wire based IMR and/or by the presence of microvascular obstruction (MVO) on CMR.
Methods.198 patients with STEMI underwent IMR and MVO assessment. Patients were classified as follows: Group1, no significant CMD (low IMR (≤40U) and no MVO); Group 2, CMD with either high IMR (>40U) or MVO; Group3, CMD with both IMR>40U and MVO. The primary endpoint was the composite of all-cause mortality, diagnosis of new heart failure, cardiac arrest, sustained ventricular tachycardia/fibrillation and cardioverter defibrillator implantation.
Results.CMD with both high IMR and MVO was present in 23.7% of the cases (Group 3) and CMD with either high IMR or MVO was observed in 40.9% of cases (Group 2). At a median follow-up of 40.1(12.8-73.8) months, the primary endpoint occurred in 34 (17%) cases. At 1-year of follow-up, Group 3 (HR=12.6, 95%CI 1.6-100.6, p=0.017) but not Group 2 (HR=7.2, 95%CI 0.9-57.9, p=0.062) had worse clinical outcomes compared with those with no significant CMD in Group 1. However, in the long-term, patients in Group 2 (HR=4.2, 95%CI 1.4-12.5, p=0.009) and those in Group 3 (HR=5.2, 95%CI 1.7-16.2, p=0.004) showed similar adverse outomes, mainly driven by the occurrence of heart failure.
Conclusion. Multimodality assessment CMD provides additional stratification of the risk of adverse events after STEMI. Post-ischaemic CMD defined by both high IMR and MVO is associated with high risk of events at 1 year after STEMI. However, in the long-term, both this group and the group with IMR>40 or MVO have a significantly higher risk of poor clinical outcome when compared with having no significant post-STEMI CMD.

Key words: ST-segment elevation myocardial infarction; Primary percutaneous coronary intervention; Coronary Microvascular Dysfunction; Microvascular obstruction; Index of microcirculatory resistance; Prognosis; Heart failure. Cardiovascular Magnetic Resonance

Abbreviation list:
CMD, Coronary microvascular dysfunction
CMR, Cardiovascular magnetic resonance
HF, heart failure
IMR, index of microcirculatory resistance
IRA, infarct-related artery
IS, infarct size
LAD, left anterior descending
LVEF, left ventricle ejection fraction
MVO, microvascular obstruction
PPCI, primary percutaneous coronary intervention
STEMI, ST segment elevation myocardial infarction
TIMI, thrombolysis in myocardial infarction

Introduction

Prompt coronary revascularization has drastically reduced the in-hospital mortality of patients with ST-segment elevation myocardial infarction (STEMI). However, the occurrence of heart failure (HF) after STEMI has not diminished and may be increasing[1, 2].

Unfortunately, suboptimal myocardial reperfusion is still observed in up to 40% of the cases despite rapid percutaneous revascularization. Post-ischaemic coronary microvascular dysfunction (CMD) plays an important role in the development of no-reflow and is a major determinant of suboptimal reperfusion[3]. Moreover, CMD is associated with larger infarct size and with a 2-fold higher risk of mortality and hospitalization for HF[4, 5].

Post-ischaemic CMD is considered a heterogenous entity and can be assessed by multiple invasive and non-invasive modalities[3] . Index of microcirculatory resistance (IMR), a pressure-wire-based and thermodilution-derived index, and microvascular obstruction (MVO) as detected on cardiovascular magnetic resonance (CMR) are the most commonly used indices for assessment of CMD after STEMI. Index of microcirculatory resistance (IMR) performed at the time of primary percutaneous coronary intervention (PPCI) has shown good accuracy in detecting MVO and in predicting large infarct size[6]. Both high IMR (>40 Units) and MVO after STEMI are associated with adverse clinical outcome including higher risk of mortality and HF[4, 5, 7].

It is unclear whether IMR and MVO describe the same pathophysiology, or whether IMR and MVO reflect distinct features of post-ischaemic CMD. Indeed, we previously reported that ~30% of patients with STEMI exhibited discordance in CMD with these two indices; they had either IMR >40 U or MVO on CMR [8] and that these patients had smaller infarct size at 6 months when compared to patients with both high IMR >40U and MVO. Therefore, we hypothesized that patients with both elevated IMR and MVO have a more severe form of post-ischaemic CMD when compared to those with either of the indices. We aimed to study

if the long-term clinical outcomes of these two groups of patients would be different from each other when compared with patients with preserved microvascular function.

Methods

Patients with STEMI admitted to the Oxford Heart Centre for PPCI were prospectively considered for enrollment in the Oxford Acute Myocardial Infarction (OxAMI) Study from 2011 to 2019. Patients who underwent post-procedural IMR assessment and CMR prior to discharge from hospital were included in this analysis. Details of the study protocols have been previously reported[6].

STEMI was diagnosed in the presence of chest pain lasting at least 30 minutes, within 12 hours from onset of symptoms, and ST-segment elevation of >2 mm (0.2 mV) in at least 2 contiguous leads on ECG. Patients were excluded in case of symptom duration longer than 12 hours, presence of severe hemodynamic instability, severe left main disease, contraindications to adenosine infusion and general contraindications to CMR.

PPCI was performed in a standard fashion and decisions about direct stenting technique, thrombectomy and glycoprotein IIb/IIIa adoption were all left to operator's discretion. All patients were loaded with dual antiplatelet therapy. Weight-adjusted unfractionated heparin or bivalirudin was adopted as antithrombotic regimen.

The study protocol was approved by the local ethics committee (REC number 10/H0408/24) and conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent.

Angiographic analysis

Coronary flow was graded using the standard TIMI criteria[9]. Angiographic thrombus score was graded from 0 to 5 after the passage of the guidewire, as previously described[10].

Myocardial blush grade at the end of the procedure was evaluated according to van't Hof[11].

Index of microcirculatory resistance

A standard pressure and temperature-monitoring guidewire (Abbott, Santa Clara, CA) was advanced in the distal segment of the culprit vessel at completion of PPCI. Coronary flow was estimated using thermodilution to derive mean transit time. Maximal hyperaemia was induced with Adenosine i.v. infusion (140 mcg/kg/min). IMR was defined as the mean distal pressure multiplied by the mean transit time at hyperaemia as previously described[6]. IMR >40 Units was considered indicative of clinically significant CMD in patients with STEMI as previously reported[6].

CMR analysis

CMR was performed using a 3.0 Tesla magnetic resonance scanner (either MAGNETOM TIM Trio or MAGNETOM Verio; Siemens Healthcare, Erlangen, Germany) within 48 hours after PPCI. The CMR protocol is described in detail in **Supplementary Material**. In 144 (72.7%) cases CMR was also performed at 6-month follow-up to assess final infarct size. Cvi42 image analysis software (Circle Cardiovascular Imaging Inc, Calgary, Canada) was used for image analysis. Left ventricular (LV) volumes and ejection fraction (EF%) were assessed from steady-state free precession images. To quantify the percentage of LV mass infarct size (IS%), as depicted by late gadolinium enhancement (LGE), the signal intensity threshold was set at 5 standard deviations above the mean SI of the remote reference myocardium[12]. The MVO was defined as the hypointense area within the LGE region and its size was quantified by manual delineation of the area.

Groups definition

CMD was defined as the presence of MVO and/or high IMR (>40 U). Patients were categorized as follows: no significant CMD with low IMR (≤ 40U) and without MVO (Group 1), CMD with either high IMR (>40U) or MVO (Group 2) and CMD with both high IMR (>40U) and MVO (Group 3).

Endpoints and definitions

The primary endpoint of the study was the composite of all-cause mortality, HF, resuscitated cardiac arrest, malignant ventricular arrhythmias (sustained ventricular tachycardia/ventricular fibrillation) and the need for a primary prevention implantable cardioverter defibrillator (ICD) .

Secondary endpoints were all-cause mortality, HF and recurrent myocardial infarction (MI). Diagnosis of HF was obtained from electronic patient records (both hospital and primary care facilities) and from OxAMI study follow up visits. HF was defined by the development of new symptoms of HF and/or prescription of diuretics with documented evidence of LV systolic dysfunction (LVEF <50%) on CMR or echocardiogram and/or raised levels of natriuretic peptide.

Statistical analysis

The normal distribution of the variables was tested using Shapiro-Wilk test and histograms. Continuous variables were reported as mean ± standard deviation or as median and interquartile range as appropriate. Categorical variables were reported as numbers and percentages. Continuous variables were compared with Student's t-test or analysis of variance with Scheffe' post hoc comparison. Mann-Whitney U test or Kruskal-Wallis test were used for non-normal distributed variables. Frequencies were compared with chi-square

test or Fisher exact test, as appropriate. Survival analysis and endpoint comparison between groups were performed with the Cox regression analysis for the calculation of hazard ratio with 95% confidence interval and the log-rank test. Kaplan Meier curves were constructed. Survival analysis of the primary endpoint was adjusted for variables with p-value <0.1 at the univariate analysis. The test for proportional-hazards assumption was applied to confirm the validity of the model.

Logistic regression analysis was performed to assess variables associated with CMD after STEMI. Multicollinearity of variables included in the final model used was assessed using variance inflation factor analysis. The validity of the model was tested using the Hosmer-Lemeshow goodness-of-fit test.

Statistical analysis was performed with Stata version 15.1 (StataCorp LLC, College Station TX). A p-value <0.05 was considered significant.

Results

Study population

Between September 2011 and September 2019, 222 patients with STEMI underwent both IMR assessment at completion of PPCI and CMR at a median time of 40.8 hours (IQR 24.7-47.8 hrs) after STEMI..

Sixteen patients were excluded because of insufficient quality of CMR imaging (n=7), gadolinium-based contrast agent not administered (n=4) or inadequate pressure-wire traces (n=5). Eight patients were lost to follow-up after hospital discharge (Supplementary Table 1). Therefore, a total of 198 patients with STEMI were included in this study. The overall characteristics of the study cohort are presented in Table1. The mean age was 60.2±10.7, 170 (85.9%) were male and 39 (19.8%) had diabetes. The median duration of follow up was 40.1(12.8-73.8) months.

IMR and MVO

High IMR (>40 U) was observed in 72 (36.4%) patients at completion of PPCI. Conversely MVO was observed in 100 (50.5%) patients.

70 (35.4%) patients had no significant CMD after STEMI (Group 1). CMD defined as presence of either high IMR or MVO (Group 2) was present in 81 (40.9%) patients (low IMR with MVO = 56 [28.3%]; high IMR without MVO = 25 [12.6%]). CMD defined as presence of both high IMR and MVO was observed in 47 (23.7%) patients (Group 3).

Significant differences in the infarcted myocardial territory and the severity of myocardial injury were observed across the groups (**Table 1-3**). In particular, patients with CMD with both high IMR and MVO (Group 3) had higher troponin release, lower coronary flow reserve, lower post-PPCI LVEF and larger IS%, both at 48 hours and at 6 months, compared with the other groups (**Table 1-3**).

On regression analysis, LAD territory infarct (OR 2.53, 95% CI 1.14-5.66, p=0.023), diabetes (OR 3.20, 95% CI 1.05-9.72, p=0.040) and impaired TIMI flow at baseline (OR 0.53, 95% CI 0.28-0.99, p=0.049) were independently associated with CMD (high IMR and/or MVO) (**Supplementary Table 2**). Predictors of Groups 2 and 3 are presented in **Supplementary Table 3-4**.

Association between post-ischaemic CMD and the extent of infarct size and systolic function impairment

Significant differences in post-PPCI LVEF% and extent of infarct size were observed across the 3 groups. Group 2 had lower LVEF% and larger IS% acutely and at 6 months compared with Group 1 with no significant CMD (**Figure 1; Table 3**), but smaller IS% at 48 hours and at 6 months and higher LVEF% at 6 months when compared with patients with Group 3 with severe CMD (**Figure 1; Table 3**).

Association between post-ischaemic CMD and the primary clinical outcome

At a median follow up time of 40.1 (12.8-73.8) months, the primary outcome occurred in 34 (17.2%) patients **(Table 4).**

Group 3 with severe CMD had a significantly higher risk of adverse events compared with patients with no significant CMD (Group 1) at 1 year (HR=12.6, 95%CI 1.6-100.6, p=0.017) and at long term follow up (HR=5.2, 95%CI 1.7-16.2, p=0.004, **Figure 2, Table 5**).

Group 2 with either high IMR or MVO showed no significant difference in the primary endpoint at 1 year of follow-up when compared with Group 1 with no significant CMD. However, the risk of long-term adverse events was significantly higher at long term follow up (**Figure 2, Table 5**).

Notably, whilst Group 2 CMD with either high IMR or MVO demonstrated a 4.2 fold increase in long-term risk when compared to Group 1 with no significant CMD, this risk was similar to Group 3 with severe CMD (HR=0.81, 95%CI 0.39-1.68, p=0.575, **Figure 2**).

In Group 2 CMD with either high IMR or MVO, there was no significant difference in the long-term clinical outcome between those patients with low IMR with MVO vs. patients with high IMR but without MVO (HR 0.82, 95%CI 0.29-2.34, p=0.715)**(Figure 3).**

CMD defined as high IMR and/or MVO was associated with the primary endpoint independently of post-PPCI TIMI flow and CMR-based infarct size (**Supplementary Table 5**). Cox regression analysis adjusted for clinical confounders is presented in **Table 5**.

Association between IMR, MVO and adverse outcomes

IMR and MVO were both associated with the primary outcome. In particular, patients with high IMR demonstrated significantly higher risk of composite adverse events (HR 2.07, 95% CI 1.06-4.07, p=0.03), heart failure (HR 2.82, 95% CI 1.23-6.46, p=0.01) and malignant ventricular arrhythmias and/or ICD implantation (HR 19.2, 95% CI 2.45-150.16, p=0.005)

(Supplementary Figure 3). Patients with MVO demonstrated significantly higher risk of composite adverse events (HR 2.46, 95% CI 1.17-5.18, p=0.02) and heart failure (HR 3.37, 95% CI 1.32-8.60, p=0.01). (Supplementary Figure 4).

All-cause mortality

All-cause mortality occurred in 15 (7.6%) cases during the study period. No significant difference was observed among patients stratified according to IMR and MVO (**Supplementary figure 3**). Age (HR=1.14, 95% CI 1.06-1.23, p<0.0001) and LVEF% (HR=0.93, 95% CI 0.88-0.97, p=0.004) were independently associated with all-cause mortality on Cox regression analysis (**Supplementary Table 6**).

Heart failure

Overall, 27 (13.6%) patients developed HF during the study period. Patients in Group 3 with severe CMD (HR=17.4, 95%CI 2.2-136.5, p=0.006) and Group 2 CMD with either high IMR or MVO (HR=12.6, 95%CI 1.6-96.6, p=0.015) demonstrated higher risk of developing HF compared with patients in Group 1 (**Supplementary Figure 4**).

Longer ischemic time (HR=1.01, 95% CI 1.00-1.02, p=0.042), LVEF% (HR=0.91, 95% CI 0.86-0.96, p<0.0001) and being in Group 3 with severe CMD (HR=17.4 95% CI 2.2-136.1, p=0.006) or Group 2 CMD with either high IMR or MVO (HR=12.6, 95% CI 1.6-96.6, p=0.015) were associated with HF at Cox regression analysis (**Supplementary Table 7**).

Recurrent Myocardial Infarction

Myocardial infarction occurred in 11 (5.5%) cases during the study period. No significant difference in the risk of recurrent infarction was observed when patients were stratified according to IMR and MVO (**Supplementary figure 5**).

The presence of diabetes (HR=8.23, 95% CI 2.05-32.95, p=0.003) and lower thrombus burden (HR=0.53, 95% CI 0.34-0.82, p=0.005) were associated with recurrent infarction on Cox regression analysis. (**Supplementary Table 8**).

Discussion

In this study, the pathophysiology of post-ischaemic CMD and its long-term prognostic implications were analyzed in patients with revascularized STEMI. We used a multimodality approach, comparing IMR and MVO, in the same patients. The principal findings are as follows:

1. When assessed with IMR and CMR, 35% had no evidence of significant CMD (Group 1) and had significantly better clinical outcomes than patients with CMD.
2. Severe CMD with high IMR and MVO (Group 3) was present in 24% of the study cohort and these patients had a larger infarct size and lower LVEF when compared to patients with CMD with either high IMR or MVO (Group 2) or patients with no evidence of CMD (Group 1). Patients in Group 3 with severe CMD had the highest risk of adverse clinical outcome at 1 year.
3. 41% of our cohort had abnormality of only one of the indices (Group 2) (either IMR >40 U or MVO). While the risk of adverse events at 1 year was not different compared with patients with no significant CMD (Group 1), in the longer term, these patients had similar outcomes to patients with the highest risk (Group 3 CMD with both high IMR and MVO). Ultimatly, they exhibited a > 4-fold higher risk of adverse outcome at long-term when compared with patients with no significant CMD at initial assessment (Group 1).

Coronary microvascular dysfunction is reported in a significant proportion of patients undergoing PPCI and it is a major determinant of adverse outcome in STEMI[4,5]. CMD is associated with suboptimal myocardial recovery and adverse LV remodeling, predisposing to both HF and ventricular arrhythmias[13, 14]. Importantly, CMD has important prognostic implications even when post-procedure TIMI flow is normal [15]. Our study found that more than 65% of patients had post-ischaemic CMD, defined by either or both IMR and CMR and that it was adversely prognostic.

Post-ischaemic CMD is a heterogenous entity and can be assessed with multiple tools. MVO on CMR and elevated IMR are the most commonly used indices of post-ischaemic CMD. A 1% increase in MVO size is associated with a 14% relative increase in mortality and an 8% increase in HF at 1 year of follow-up[7]. IMR has been extensively validated to predict infarct size and clinical outcomes including mortality and hospitalization for HF in patients with STEMI[4, 5].

However, it is unclear which of either CMR or invasive physiology or even both should be used to risk stratify patients with CMD early after STEMI and how it should alter the clinical management. Our study is the first to show that combining MVO and IMR, may offer incremental long-term risk stratification compared to assessments of MVO and IMR in isolation. Although this will require further investigations to be confirmed, implementing this approach in the clinical setting could represent an important step towards personalized precision medicine. In particular, patients identified with CMD may benefit from being followed up regularly in order to aggressively optimize medical therapy and promptly detect and treat the onset of heart failure (Central Figure). The effectiveness of this approach and its implications on health care systems will need to be tested in adequately powered studies.

In a proportion of patients with STEMI, IMR (≤40 or >40 U) can be discordant from the presence (or absence) of MVO at CMR[8]. In a previous study, we showed that patients with

both MVO and IMR>40 U presented an 11.9-fold increased risk of having IS larger than 25% of the myocardial mass at 6 months follow up[7]. Similarly, patients with either IMR>40 or MVO showed a larger IS at 6 months compared with patients with no MVO and preserved IMR ≤40 U[8]. Moreover, IMR ≤40U appeared associated with a favourable reduction of the infarct size at six months, irrespective of MVO, suggesting the possibility that IMR could offer complementary information to CMR, in assesing the severity of post-ischaemic CMD[8].
In the present study, we observed that, when compared to patients with either IMR>40 or MVO (Group 2), patients with IMR >40 and MVO (Group 3) have larger infarcts both acutely and at 6 months. However, this study, looking at long term events, shows that the patients with either high IMR or MVO, defined here as Group 2 CMD, also had adverse clinical outcomes similar to Group 3 with severe CMD (with both high IMR and MVO) at a median follow up of 40 months (3.3 years).
This implies that the multi-faceted pathophysiology of CMD, when detected by either IMR or MVO after PPCI for STEMI, may continue to drive adverse changes in the myocardium and cardiac function, with lasting effects translating into adverse clinical events beyond 6 months.

The difference in the primary endpoint between groups was mainly driven by the development of HF at follow up and there was no difference in all-cause mortality.
These observations on long-term clinical outcomes further confirm and extend the previously reported effect of combined IMR and MVO on IS and left ventricular remodelling at 6 months post-STEMI[7]. However, contrary to previous speculation that patients with discordant IMR and MVO could represent a group of patients with moderate CMD and therefore at intermediate risk, this study suggests that this is only partially true. This is because patients in this group tend to develop HF after the first year and, eventually, at long term, a prognosis not dissimilar from those of patients with both IMR>40 and MVO at

completion of PPCI. Our data suggest that these patients should be carefully followed-up and considered at risk of developing late HF.

We previously observed that in patients where the IMR is preserved, even in presence of MVO, a significant regression of the infarct size over time is possible, whereas in patients with an IMR above 40 Units, the microvasculature in the infarct zone appeared to be irreversibly damaged[8]. Inevitably, IMR and MVO are dynamic processes and the extent of any abnormality will regress after the acute phase of STEMI. Consideration of our data suggests that MVO represents a severe perfusion defect and a profound marker of microvascular injury, especially when associated with intramyocardial hemorrhage.

On the other hand, IMR measured acutely is probably a combination of reversible stunning the of the microcirculation and irreversible damage related to the ischemia and reperfusion injury and/or distal embolization. Notably, IMR and MVO can reflect residual CMD and the disintegrity of the watershed zones adjacent to the infarct core, which are ultimately responsible for the final extent of the infarct size. It is also possible that an elevated IMR measured post infarct could contain a proportion of pre-existing CMD and it may not be entirely be related to the acute ischemic injury[3].

By offering a good compromise between ease of use and diagnostic accuracy, IMR is becoming the preferred method for the assessment of microvascular status in the catheterization laboratory. Based on our study, IMR should be measured immediately post PPCI to detect clinically significant CMD. Our study also supports the use of CMR to detect MVO. If either or both are found, the patient can diagnosed with clinically significant and prognistically important post-ischaemic CMD. In such cases, close long-term follow up should be initiated to detect and treat the onset of heart failure (Central illustration).

Limitations

This is a single centre study with a relatively small sample size. Importantly, further large dedicated studies are warranted to confirm these observations. Nevertheless, this is the largest report available in which post-ischaemic CMD has been assessed using a multimodality approach in the same patient, including invasive physiology and CMR assessment of MVO. Secondly, the survival analysis was conducted using a time-to-first-event approach. Therefore, the risk of having subsequent multiple events was not analysed in this study. Furthermore, the OxAMI study was not designed to detect differences in mortality between subgroup of patients stratified according to IMR and MVO.

In this study only HF with reduced ejection fraction has been considered, as systolic dysfunction is the predominant phenomenon after STEMI and due to the overwhelming evidence that post-ischaemic CMD is contributory. However, it is possible that pre-existing CMD may have caused worse haemodynamic profile and high filling pressures in our patients with STEMI as previously reported in patients with HF with preserved ejection fraction(HFpEF)[16].

Conclusion

The presence of CMD post-myocardial infaction, predicts a more than 4-fold increase in long-term risk of adverse outcomes, which is mainly driven by the occurrence of heart failure. Importantly, patients with abnormality of either one of the CMD indices (Group 2: IMR >40 U or MVO) also presented a similar long-term risk of adverse outcome compared with patients with neither elevated IMR and MVO (Group 1).

Conflict of interest: none

Competency in Medical Knowledge

CMD is a well-established complication of STEMI. When characterised with both invasive physiology and CMR, ~2/3 of patients show concordance between indices of CMD (IMR≤40U and no MVO or IMR >40U and MVO) whilst ~1/3 of patients have a discordant picture with either abnormal IMR (and no MVO) or evidence of MVO (and an IMR<40). In patients who undergo Primary Percutaneous Intervention (PPCI) for STEMI, the presence of *either* post procedural IMR >40 or MVO carry similar long-term adverse outcomes to those with the presence of both. This is mainly due to the occurence of new heart failure in both groups.

Translational outlook

Effective stratification of high-risk patients after ST segment elevation myocardial infarction (STEMI) can allow for the provision of precision medicine. The current work ultimately provides evidence of the additional prognostic value of an integrated definition of coronary microvascular dysfunction (CMD) with both CMR and invasive coronary physiology after primary percutaneous coronary intervention. When combined together, MVO on CMR and the invasively measured IMR can identify early patients at high risk of developing heart failure at 1 and 4 years, thus allowing clinicians to tailor additional therapies and/or closer follow-ups. At the same time, this integrated approach can provide an optimal platform for research in the development and testing of future therapies for CMD in patients with STEMI.

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Figure legends

Figure 1. Left ventricular ejection fraction and Infarct size in patients stratified according to IMR and MVO
Box plots of LVEF% and IS% at 48 hours and 6 months in patients stratified according to IMR and MVO.

Figure 2. Survival analysis of the primary endpoint
Kaplan-Meier curves of patients stratified according to IMR and MVO at 1 year (a) and at long term (b). Hazard ratios for patients with IMR >40 U and MVO (Group 3) and for those with either high IMR or MVO (Group 2) are provided in comparison with patients with no significant CMD (Group 1).

Figure 3. Survival analysis of the subgroups with either elevated IMR or MVO
Kaplan-Meier curves of patients stratified according to IMR and MVO at 1 year (a) and at long term(b). Hazard ratios for patients are provided in comparison with patients with no significant CMD (Group 1).

Central illustration. Proposed risk stratification pathway post PPCI
IMR is measured post PCI in the catheterization laboratory. CMR is performed before hospital discharge. If both IMR>40 U and MVO are present patient should be considered at high risk of adverse outcomes both in the short and long terms. If either are present, they should be considered at high risk in the long term. Both of these groups (2 and 3) should be given ‘enhanced care’; with close and regular clinical follow up, optimal medical therapy and prompt treatment for heart failure upon detection.

Table 1. Overall clinical characteristics

Variable	Overall	Group 1 (No significant CMD)	Group 2 (CMD with high IMR or MVO)	Group 3 (CMD with high IMR and MVO)	p-value
No. patients	198(100)	70(35.4)	81(40.9)	47(23.7)	
Age, years	60.2±10.7	59.2±11.6	61.5±10.2	59.3±10.4	0.352
Male sex, %	170(85.9)	59(84.3)	68(83.9)	43(91.5)	0.446
Hypertension, %	88(44.9)	31(44.9)	40(50.0)	17(36.2)	0.318
Hypercholesterolemia, %	65(38.5)	18(25.7)	30(37.0)	17(36.2)	0.485
Diabetes, %	39(19.8)	9(12.9)	21(26.5)	9(19.1)	0.120
Smoking, %	72(36.7)	35(50.7)	25(31.2)	12(25.5)	**0.009**
eGFR, ml/min/1.73m^2	92.4(72.7-105.7)	97.9(78.9-111.3)	88.2(73.5-97.9)	92.3(74.4-99.1	0.122
Pain-to-balloon time, min	183(125-347)	196(133-360)	166(110-314)	215(142-322)	0.058
Troponin*	1200(301-2776)	445(121-1179)	1342(547-3135)	1752(1131-6387)	**0.0001**

eGFR, estimated glomerular filtration rate

*Magnitude of troponin release defined as the multiple of upper limit of normal reference

Table 2. Angiographic, procedural and physiology data

Variable	Overall	Group 1 (No significant CMD)	Group 2 (CMD with high IMR or MVO)	Group 3 (CMD with high IMR and MVO)	p-value
Infarct related artery					
LAD	98(49.5)	26(37.1)	42(51.9)	30(63.9)	
LCX	21(10.6)	6(8.6)	8(9.9)	7(14.9)	**0.028**
RCA	75(37.9)	36(51.4)	30(37.0)	9(19.1)	
Diagonal	4(2.0)	2(2.9)	1(1.2)	1(2.1)	
TIMI flow at baseline					
TIMI=0	148(74.7)	43(61.4)	66(81.5)	39(83.0)	
TIMI=1	17(8.6)	6(8.7)	7(8.6)	4(8.5)	**0.003**
TIMI=2	19(9.6)	9(12.8)	6(7.4)	4(8.5)	
TIMI=3	14(7.1)	12(17.1)	2(2.5)	0(0.0)	
TIMI flow post-PCI					
TIMI=0	0(0.0)	0(0.0)	0(0.0)	0(0.0)	
TIMI=1	3(1.5)	1(1.4)	0(0.0)	2(4.2)	**<0.0001**
TIMI=2	24(12.1)	1(1.4)	10(12.2)	13(27.7)	
TIMI=3	171(86.4)	68(97.2)	71(87.8)	32(68.1)	
Stent length, mm	29.1±13.7	30.1±15.9	28.7±11.0	28.6±14.7	0.817
Stent diameter, mm	3.47±0.46	3.41±0.47	3.48±0.42	3.52±0.52	0.589
Post-PPCI Coronary physiology					
Pd/Pa	0.95±0.05	0.96±0.05	0.95±0.05	0.95±0.05	0.321
FFR	0.93±0.06	0.92±0.06	0.93±0.06	0.93±0.07	0.484
Mean transit time	0.41(0.27-0.73)	0.28(0.20-0.42)	0.35(0.28-0.57)	0.87(0.55-1.32)	**<0.0001**
CFR	1.58(1.18-2.28)	1.99(1.49-2.69)	1.70(1.30-2.29)	1.10(1.00-1.48)	**<0.0001**
IMR	31.7(20.0-50.5)	20.0(14.6-31.0)	28.7(21.0-44.02)	69.6(46.2-100.2)	**<0.0001**

CFR, coronary flow reserve; FFR, fractional flow reserve; IMR, index of microcirculatory resistance; LAD, left anterior descending artery; LCX, left circumflex artery; Pa, aortic pressure; Pd, distal coronary pressure; RCA, right coronary artery; TIMI, thrombolysis in myocardial infarction.

Table 3. Cardiovascular magnestic resonance data within 48 hours from STEMI and at 6 months

	Group 1 (No significant CMD)	**Group 2 (CMD with high IMR or MVO)**	**Group 3 (CMD with high IMR and MVO)**	**p-value (overall)**	**p-value Group1 vs Group2**	**p-value Group1 vs Group3**	**p-value Group2 vs Group3**
CMR within 48 hours							
Time from PPCI, hours	39.6(23.5-46.8)	41.0(28.3-48.7)	31.2(22.6-43.9)	0.121	0.661	0.484	0.121
EDVi, ml/m^2	77.0±19.2	77.6±18.9	87.3±18.5	**0.010**	0.983	**0.020**	**0.025**
ESVi, ml/m^2	37.7±12.6	42.6±15.7	49.9±14.9	**<0.0001**	0.117	**<0.0001**	**0.028**
LVEF, %	51.4±8.5	46.0±10.1	43.2±8.8	**<0.0001**	**<0.0001**	**<0.0001**	0.114
IS%	17.1±10.1	29.9±12.9	35.5±11.8	**<0.0001**	**<0.0001**	**<0.0001**	**0.008**
MVO%	0(0-0)	1.0(0.0-3.7)	4.0(2.2-8.6)	**0.0001**	**<0.0001**	**<0.0001**	**<0.0001**
CMR at 6 months							
EDVi, ml/m^2	76.0±15.5	81.4±17.8	94.3±24.1	**<0.0001**	0.326	**<0.0001**	**0.008**
ESVi, ml/m^2	31.6±10.8	39.4±14.7	51.2±21.1	**<0.0001**	**0.036**	**<0.0001**	**0.003**
LVEF, %	59.0±7.7	52.9±8.8	45.8±10.5	**<0.0001**	**0.001**	**<0.0001**	**<0.0001**
IS%	9.7±9.4	20.8±11.2	26.9±10.7	**<0.0001**	**<0.0001**	**<0.0001**	**0.006**

EDVi, end diastolic volume index; ESVi, end systolic volume index; LVEF, left ventricle ejection fraction; IS, infarct size; MVO, microvascular obstruction.

Table 4. Adverse clinical events at follow up

	Overall	**Group 1 (No significant CMD)**	**Group 2 (CMD with high IMR or MVO)**	**Group 3 (CMD with high IMR and MVO)**	**p-value**
No. Patients	198(100.0)	70(35.4)	81(40.9)	47(23.7)	
Primary endpoint	34(17.2)	4(5.7)	18(22.2)	12(25.5)	**0.016**
All cause death	15(7.6)	4(5.7)	8(9.9)	3(6.4)	0.080
Cardiac death	6(3.0)	1(1.4)	3(3.7)	2(4.2)	0.459
Heart failure	27(13.6)	1(1.4)	15(18.5)	11(23.4)	**0.003**
VT/VF	11(5.5)	0(0.0)	4(4.9)	7(14.9)	**0.001**
ICD	5(2.5)	0(0.0)	2(2.5)	3(6.4)	0.153

ICD, implantable cardiac defibrillator; VF, ventricular fibrillation; VT, ventricular tachycardia.

Table 5. Cox Regression analysis of the primary endpoint				
	Univariate		**Multivariate**	
Variable	**HR (95%CI)**	**p-value**	**HR (95%CI)**	**p-value**
Age, years	1.04(1.01-1.07)	**0.018**	1.04(1.01-1.08)	**0.037**
Male sex	0.65(0.28-1.50)	0.319	0.82(0.30-2.26)	-
Smoker	0.58(0.26-1.29)	0.184	1.22(0.50-2.99)	-
Diabetes	1.35(0.61-2.99)	0.462	1.54(0.68-3.52)	-
LAD	1.27(0.65-1.50)	0.483	1.15(0.53-2.49)	-
Ischemic time	1.00(1.00-1.01)	**0.041**	1.00(0.99-1.01)	0.144
Troponin (peak)§	1.00(0.99-1.01)	0.721	1.00(0.99-1.01)	-
Post-PCI TIMI flow	0.39(0.22-0.68)	**0.001**	0.74(0.37-1.49)	0.405
Group2 (IMR>40U or MVO)	4.24(1.43-12.52)	**0.009**	4.69(1.36-16.15)	**0.014**
Group3 (IMR>40U and MVO)	5.22(1.68-16.21)	**0.004**	6.80(1.83-25.22)	**0.004**
HR, hazard ratio; LAD, left anterior descending artery; IMR, index of microcirculatory resistance; MVO, microvascular obstruction; TIMI, thrombolysis in myocardial infarction. **§**Magnitude of troponin release defined as the multiple of upper limit of normal reference				