EuroIntervention 2015;11:518-524 published online ahead of print April 2015

Myocardial perfusion grade predicts final infarct size and left ventricular function in patients with ST-elevation myocardial infarction treated with a pharmaco-invasive strategy (thrombolysis and early angioplasty)

Anne Bethke[1]*, MD; Sigrun Halvorsen[2,5], PhD; Ellen Bøhmer[3], PhD; Michael Abdelnoor[4], PhD; Harald Arnesen[2,4,5], PhD; Pavel Hoffmann[6], PhD

1. Department of Radiology and Nuclear Medicine, Division of Diagnostics and Intervention, Oslo University Hospital, Ullevål, Norway; 2. Department of Cardiology B, Oslo University Hospital, Ullevål, Norway; 3. Department of Medicine, Innlandet Hospital Trust, Lillehammer, Norway; 4. Centre for Clinical Research, Oslo University Hospital, Ullevål, Norway; 5. Faculty of Medicine, University of Oslo, Oslo, Norway; 6. Section for Interventional Cardiology, Department of Cardiology, Division of Cardiovascular and Pulmonary Diseases, Oslo University Hospital, Ullevål, Norway

KEYWORDS

- acute myocardial infarction
- fibrinolytic therapy
- left ventricular function
- magnetic resonance imaging
- percutaneous coronary intervention
- TMP grade

Abstract

Aims: Primary percutaneous coronary intervention (PCI) for ST-elevation myocardial infarction (STEMI) usually restores TIMI 3 flow in the occluded artery, but microvascular impairment may persist in >30% of patients. Less is known about microvascular reperfusion in STEMI patients treated with thrombolysis followed by early PCI. We aimed to assess the association between TIMI myocardial perfusion (TMP) at the end of the PCI procedure and left ventricular function (LVEF) and infarct size after three months in such patients.

Methods and results: Patients with STEMI treated with thrombolysis and early PCI were included. TMP grade was assessed at the end of the PCI procedure, and MRI was performed after three months. Of the 89 patients included, 92% (n=82) had TIMI 3 flow at the end of the PCI procedure, while only 62% (n=55) had TMP grade 2 or 3. Patients with TMP grade 2-3 had significantly higher LVEF (59% [53-67] vs. 50% [41-56], p<0.0001) and smaller infarct size (8.3 ml [2.7-15.5] vs. 20.7 ml [13.0-36.0], p<0,0001) after three months.

Conclusions: In STEMI patients treated with thrombolysis and early PCI, the TMP grade at the end of the PCI procedure was significantly associated with LVEF and infarct size after three months.

Corresponding author: Department of Radiology and Nuclear Medicine, Division of Diagnostics and Intervention, Oslo University Hospital, Ullevål, 0407 Oslo, Norway. E-mail: annbet@ous-hf.no

SUBMITTED ON 07/08/2014 - REVISION RECEIVED ON 03/12/2014 - ACCEPTED ON 22/12/2014

DOI: 10.4244/EIJY15M04_02

Introduction

Primary percutaneous coronary intervention (PCI) is the preferred reperfusion strategy in ST-elevation myocardial infarction (STEMI), but, in areas with transfer times of more than 90-120 min to PCI, initial thrombolysis remains the treatment of choice[1]. Immediate transfer for early angioplasty after thrombolytic therapy has been shown to improve outcome compared with thrombolysis alone[2], and has shown similar efficacy and safety results to those of primary PCI in areas with long transfer delays[3,4].

Angiographic successful reperfusion in STEMI has been defined as TIMI (Thrombolysis In Myocardial Infarction) 3 flow in the epicardial artery[5]. However, complete restoration of epicardial flow does not necessarily translate into flow restoration on the myocardial level or to microvascular reperfusion, and normal tissue perfusion may be obtained in only 25-55% of the patients[6,7]. In 1994, the first studies demonstrated a correlation between coronary flow reserve and regional myocardial function on angiography[8].

TIMI myocardial perfusion (TMP) grade provides important prognostic information beyond epicardial flow[6,7,9-11]. Full reperfusion at the myocardial level is as important as restoration of TIMI 3 flow, and is an independent predictor of myocardial function recovery and long-term survival[12-14]. The importance of myocardial reperfusion in STEMI patients treated by thrombolysis followed by early PCI has previously been assessed by left ventriculography[11], and recent studies have indicated that TMP grade correlates with both the presence and the extent of early and late microvascular obstruction (MVO) on magnetic resonance imaging (MRI)[15].

Due to its high spatial resolution, high accuracy and reproducibility, MRI is considered the gold standard for measuring left ventricular ejection fraction (LVEF) and volumes[16,17]. Further, late enhancement imaging 10-30 min after contrast administration offers a precise method to distinguish and quantify the size and transmurality of infarcted myocardium with better sensitivity and reproducibility than echocardiography and scintigraphy[16,18].

The aim of this study was to assess the relationship between TMP grade at the end of the PCI procedure and MRI-determined LVEF and infarct size after three months in STEMI patients treated with thrombolysis followed by early PCI.

Methods

PATIENTS AND STUDY DESIGN

This was a pre-specified substudy of the NORwegian study on DIstrict treatment of ST Elevation Myocardial Infarction (NORDISTEMI)[19,20]. The study design and clinical results have been published previously[20]. In brief, patients with STEMI of less than 6 hrs duration and more than 90 min expected time delay to primary PCI received full-dose thrombolysis and were randomised to transfer for immediate coronary angiography and intervention if indicated (early invasive group), or managed conservatively in the local hospital. Patients in the conservative group were referred for urgent angiography only if there was persistent chest pain or <50% reduction of ST-segment elevation 60 min after initiation of thrombolysis (rescue indication), or if there was haemodynamic instability. In the present substudy, patients from both groups being treated by thrombolysis followed by early PCI, and being able and willing to undergo cardiac MRI, were included.

TIMI flow was assessed prior to and after the PCI procedure, and TMP grade was assessed at the end of the PCI procedure. All patients were evaluated by MRI after three months.

Reasons for not being able to undergo MRI after three months were death (n=6), disabling stroke, pacemaker, claustrophobia or refusal to make the journey to the imaging centre (100-400 km). Patients with known renal impairment or development of renal dysfunction during hospitalisation were also excluded because of potential toxicity related to gadolinium use[21].

All patients provided written informed consent in accordance with the revised Declaration of Helsinki before enrolment. The study was approved by the Regional Ethics Committee for Medical Research and registered at the website www.clinicaltrials.gov, NCT00161005.

CORONARY ANGIOGRAPHY AND TMP GRADE

PCI was performed as a standard procedure. The choice of stent type and the use of glycoprotein IIb/IIIa inhibitors and referral for surgery in case of left main coronary artery disease or serious three-vessel disease were left to the judgement of the operator.

The TMP grade was assessed at the end of the PCI procedure. After intracoronary injection of 200 µg glycerol trinitrate, coronary angiography was performed using Ioversol 350 mg I/ml (Optiray®; Covidien Deutschland GmbH, Neustadt, Germany). The TMP grades were defined as 0 to 3 according to the method of Gibson et al[9]. For comparison and analysis, patients were divided into two groups in accordance with previous studies[14]: Group I=TMP grade 0 or 1 and Group II=TMP grade 2 or 3. TMP grading was done by an observer blinded to clinical results.

CARDIAC MAGNETIC RESONANCE IMAGING

Cardiac magnetic resonance imaging was performed in a 1.5T whole-body scanner (Philips Intera; Philips Medical Systems, Best, The Netherlands), using a five-element synergy-cardiac coil as previously described[6].

Image analysis was performed on a View Forum workstation (Philips Medical Systems). End-diastolic and end-systolic volumes (EDV, ESV), LVEF and left ventricular myocardial volume were calculated by assessment of the short-axis images. Myocardial first-pass perfusion was analysed by measuring the signal intensity vs. time. Signal intensity was measured in the region of the infarction and in remote, not infarcted myocardium. Maximum contrast enhancement and time to peak were analysed.

Infarct size was assessed in the delayed enhancement images. The infarct volume was reported in ml and as percent of total left ventricular myocardium volume. The cut-off for large infarct size was defined as the 75th percentile in accordance with previous studies[22-25]. The observer conducting the image analysis was blinded to clinical data. The intraobserver variation coefficients for EDV and LVEF were 2.5 and 3.8%, respectively. The intraobserver variation coefficient for estimation of total infarct volume was 10.2%.

CLINICAL FOLLOW-UP

Cardiovascular events in terms of death, reinfarction, stroke and new ischaemia within the first year after the infarction were collected as part of the main protocol of the NORDISTEMI study[19].

DESIGN AND STATISTICAL ANALYSIS

This substudy was a cohort study of exposed (TMP grade 0-1) versus unexposed (TMP grade 2-3) patients with the outcomes large infarct (defined as >75th percentile, 17.7%) and impaired left ventricular ejection fraction (<40%).

Analyses of effect modifiers and quantification of confounders were performed by stratification analysis. Confounding effects were quantified by comparing the crude odds ratio (OR) to the adjusted Mantel-Haenszel OR (ORmh). Effect modification was estimated by the Breslow-Day test of heterogeneity in the stratification procedure. Control for multiple confounders was performed by the multivariate logistic model and estimation of multiple interactions using the logistic likelihood ratio test[26].

Receiver operating characteristic (ROC) curve analysis was performed for the ability of TMP to discriminate large infarct size and impaired LVEF. Estimated area under the curve (AUC) >0.75 indicates a good discriminatory effect of TMP grade on the outcomes large infarct size and low LVEF. A test of significance against an AUC=0.5 diagonal null hypothesis of non-discriminatory effect was performed.

Continuous variables were presented as medians with interquartile range. As several data were skewed, the Mann-Whitney U test was used for group comparison of continuous data. Categorical data were given as numbers and percentages, and analysis was performed using the chi-square test or Fisher's exact test when appropriate.

Statistical analysis was performed using Epi Info™ version 3.3.2 (CDC, Atlanta, GA, USA). A p-value of <0.05 was considered statistically significant.

Results

Eighty-nine of the 266 patients included in the NORDISTEMI study were enrolled in this substudy, 71 from the early invasive group and 18 rescue patients from the conservative group. TIMI flow grade 3 was observed before PCI in 48 patients, and after PCI in 82 patients (92%). TMP grade after PCI was as follows: TMP grade 0 in 3 patients, TMP grade 1 in 31 patients, TMP grade 2 in 27 patients, and TMP grade 3 in 28 patients. The patients were divided into two groups depending on their TMP grade after PCI: Group I, TMP grade 0 and 1 (n=34), and Group II, TMP grade 2 and 3 (n=55). Baseline characteristics according to TMP group are shown in **Table 1**.

Patients with TMP grade 0-1 had a longer time from thrombolysis to angiography. There were no significant differences in infarct-related artery (LAD vs. LCX and RCA) between groups. More patients in Group II had TIMI 3 flow before PCI (60% vs. 40%). Significantly more patients in Group II had TIMI 3 flow after the procedure **(Table 1)**. Patients in Group I had significantly higher values of troponin T at 67 hrs.

Table 1. Selected characteristics of the study population.

	TMP grade 0-1 (n=34) Group I	TMP grade 2-3 (n=55) Group II	*p*-value
Age (years)	56 (53-62)	58 (51-66)	0.47
Male gender	28 (82%)	47 (85%)	0.70
Immediate angiography group	24 (71%)	47 (85%)	0.09
Rescue PCI group	10 (29%)	8 (15%)	
Previous PCI	2 (6%)	5 (9%)	0.58
Previous myocardial infarction	4 (12%)	6 (11%)	0.90
Previous CABG	1 (3%)	2 (4%)	0.89
Treated hypertension	14 (41%)	7 (13%)	0.002
Diabetes mellitus	1 (3%)	2 (4%)	0.89
Hyperlipidaemia	7 (21%)	7 (13%)	0.32
Current/previous smoker	24 (71%)	42 (76%)	0.54
Anterior infarction (LAD)	15 (44%)	20 (36%)	0.47
Single-vessel disease	27 (79%)	33 (60%)	0.058
TIMI 3 flow pre PCI	14 (41%)	34 (62%)	0.058
TIMI 3 flow post PCI	27 (79%)	55 (100%)	<0.001
Symptom onset to lysis (min)	108 (80-175)	112 (76-175)	0.87
Time from lysis to angio (min)	155 (140-203)	126 (105-171)	0.013
Troponin T release at 67 hrs (µg/L)	3.2 (1.8-4.9)	1.8 (0.8-2.6)	0.002

Data are median and interquartile range or numbers and percentage. CABG: coronary artery bypass graft; LAD: left anterior descending artery; PCI: percutaneous coronary intervention; TMP: TIMI myocardial perfusion

No significant differences were found between TMP groups in first-pass perfusion of the myocardium by MRI after three months. In both groups, maximum contrast enhancement and maximum contrast enhancement/time to peak were significantly reduced in the infarcted area compared to normal, remote myocardium (data not shown).

Patients with TMP grade 2-3 post PCI had significantly lower EDV, higher LVEF and better regional wall thickening in the infarcted region, and these patients also had significantly smaller infarct sizes **(Table 2)**.

In a supplementary analysis, infarct size and LVEF were studied in relation to TIMI flow prior to PCI. When patients with TIMI flow

Table 2. Cardiac magnetic resonance imaging. Structural and functional data of the left ventricle and infarct volumes three months after infarction as related to the TMP grade.

	TMP grade 0-1	TMP grade 2-3	*p*-value
EDV (ml)	180 (160-217)	154 (131-196)	0.036
ESV (ml)	88 (66-128)	61 (47-88)	0.0003
LVEF (%)	50 (41-56)	59 (53-67)	<0.0001
ED wall thickness in infarcted region (mm)	5.2 (4.3-6.2)	6.0 (5.3-7.3)	0.006
Wall thickening in infarcted region (%)	16 (3.4-28)	42 (21-81)	<0.0001
Infarct volume (ml)	20.7 (13.0-36.0)	8.3 (2.7-15.5)	<0.0001
LV myocardial volume (ml)	124 (108-145)	125 (101-140)	0.87
Relative infarct volume (%)	18.2 (10.3-25.7)	7.1 (2.9-11.3)	<0.0001

Data are median values and interquartile range. ED: end-diastolic; EDV: end-diastolic volume; ESV: end-systolic volume; LV: left ventricle; LVEF: left ventricular ejection fraction; TMP: TIMI myocardial perfusion

0, 1 and 2 (n=41) were compared with patients with TIMI 3 flow (n=48) prior to PCI, no significant differences were found in infarct size (11% [8-16] vs. 9% [4-19], p=0.47) or in LVEF (55% [47-60] vs. 57% [52-65], p=0.22) .

The prevalence of large infarct size and low LVEF in our population was 23/89 (25.8%) and 11/89 (12.4%), respectively. The patients with TMP grade 0-1 had an 11.2 times higher risk of developing large infarctions (95% confidence interval [CI]: 3.6-35.1, p<0.0001) and a 5.3 times higher risk of developing low LVEF (95% CI: 1.3-21.8, p=0.011).

Adjusting for potential confounders (hypertension, time from thrombolysis to angiography, TIMI flow at angiography, TIMI flow post PCI and belonging to the rescue PCI group) using a multivariate logistic model changed the results significantly. Adjusted OR (ORa) and 95% CI was 34.0 (6-185) for developing large infarctions, and 6.7 (6-185) for developing low LVEF, in patients with TMP 0-1 compared to TMP 2-3 **(Table 3)**.

ROC curve analysis evaluating TMP grade 0-1 as a test for discriminating large relative infarct size (>17.7%) and impaired left ventricular function (LVEF <40%) is shown in **Figure 1A** and **Figure 1B**. For discriminating large infarct size, AUC was 0.77 (95% CI: 0.67-0.85, p=0.0001), and, for LVEF <40%, AUC was 0.69 (95% CI: 0.58-0.78, p=0.03).

Table 3. Stratification analysis to evaluate effect modification and quantify confounders. TMP grade after PCI is the exposition variable and the outcome is (A) large myocardial infarction (>17.7%) and (B) low ejection fraction (<40%).

(A) Large infarct size			
Variable controlled	**ORmh (95% CI)**	**Hetero-geneity**	**Confounding effect (%)**
1 - Hypertension	12.7 (3.8-42.9)	No	13.3
2 - Time thrombolysis to angiography	18.6 (4.2-81.4)	No	66.1
3 - Reduced TIMI flow pre PCI (0, 1 & 2)	16.8 (4.6-61.1)	No	50.0
4 - Reduced TIMI flow post PCI (0, 1 & 2)	12.5 (3.8-41.1)	No	11.6
5 - Rescue PCI	10.6 (3.9-33.0)	No	–4.5
Control for multiple confounders using the multivariate logistic model			
Variables controlled	**ORa (95% CI)**	**Hetero-geneity**	**Confounding effect (%)**
1, 2 & 3	34.0 (6.3-185)	No	200
(B) Low ejection fraction			
Variable controlled	**ORmh (95% CI)**	**Hetero-geneity**	**Confounding effect (%)**
1 - Hypertension	5.9 (1.3-25.8)	No	11.3
2 - Time thrombolysis to angiography	6.5 (1.1-39.1)	No	22.6
3 - Reduced TIMI flow pre PCI (0, 1 & 2)	5.2 (1.2-22.0)	No	1.8
4 - Reduced TIMI flow post PCI (0, 1 & 2)	4.9 (1.1-21.6)	No	7.5
5 - Rescue PCI	4.8 (1.2-20.1)	No	–9.4
Control for multiple confounders using the multivariate logistic model			
Variables controlled	**ORa (95% CI)**	**Hetero-geneity**	**Confounding effect (%)**
1, 2 & 5	6.7 (6.3-185)	No	26.4

ORa: adjusted odds ratio for multiple confounders; ORmh: adjusted Mantel-Haenszel odds ratio controlled for one variable; PCI: percutaneous coronary intervention; TIMI: Thrombolysis In Myocardial Infarction

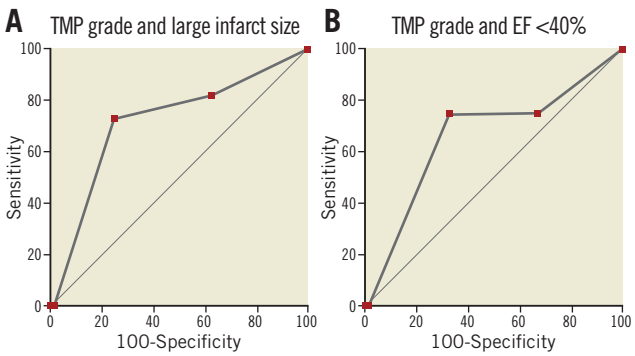

Figure 1. *ROC curve analysis for large myocardial infarction and for impaired LVEF. ROC curve analysis for TMP grade after PCI as a diagnostic test of large myocardial infarction (>17.7%, 75th percentile) (A), and impaired LVEF (<40%) (B), evaluated by MRI at three months after STEMI.*

A total of 15 out of 89 patients experienced a cardiovascular event (reinfarction, stroke or new ischaemia) within the first year after the index infarction: six out of 34 patients in the TMP grade 0-1 group (17.6%) and 9/55 in the TMP grade 2-3 group (16.4%). None of the patients died.

Discussion

The present study addresses the ability of the TMP grade at the end of a PCI procedure to predict large infarctions or reduced LVEF, in patients with STEMI treated with thrombolysis followed by early PCI. Both LVEF and infarct size were assessed by MRI three months after the infarction. The results suggested that TMP grade post PCI is an important predictor of both LVEF and infarct size in STEMI patients treated by a pharmaco-invasive strategy. Patients with TMP grade 0-1 had significantly higher OR for developing large infarctions (>17.7% of the left ventricle) and low LVEF (<40%) compared to patients with TMP grade 2-3. Our data are in agreement with previous studies performed in STEMI patients treated by thrombolysis[11]. Our study demonstrates that the time delay from thrombolysis to angiography was an important confounder for the predictive effect of TMP grade, both on infarct size and LVEF. These findings are in agreement with previous results showing that TIMI flow 2 or less and myocardial blush grade (MBG) 0 and 1 were associated with time delay pre PCI, and also associated with increased end-diastolic and end-systolic volumes at follow-up[15,27].

In 2008, Pride et al[28] showed reduced morbidity and mortality in STEMI patients with high angiographic perfusion score, which combines TIMI flow grade and TMP grade, treated with late PCI following fibrinolytic therapy. Our finding is contrary to the study of Wong et al[15] which did not show a correlation between TMP grade and LVEF after three months. This might be due to their smaller study population and a slightly different definition of impaired myocardial perfusion at PCI. Furthermore, they included solely patients who underwent primary PCI[15].

In a recent study on TMP grade after late recanalisation (>24 hours) of infarct-related arteries, moderate improvements in LVEF in patients with both perfusion grade 0-1 and grade 2-3 were found, but there was no significant difference between the groups[29]. In the present study on patients treated with early PCI after thrombolysis, the patients with TMP grade 2-3 had significantly better regional wall function, global LVEF and smaller infarct volumes after three months. The reason for this discrepancy is not clear, but we might speculate that, with late infarct artery recanalisation, the predictive ability of the TMP grade post PCI on LVEF is reduced or lost. Our finding that time delay from thrombolysis to PCI was an important confounder for the predictive effect of TMP grade supports this explanation. Furthermore, both during primary PCI and early post PCI for STEMI there is an evolution of MBG and TMP grade, and it is the final perfusion outcome that is best correlated to remodelling, LV function and even to mortality[27,30].

TMP grade 0-1 was associated with larger left ventricular end-diastolic and end-systolic volumes, and reduced diastolic wall thickness and reduced systolic wall thickening in the infarcted region. These data indicate favourable left ventricular remodelling in patients with restored myocardial perfusion (TMP grade 2-3).

Normalised epicardial blood flow after STEMI as assessed by TIMI flow grades has been related to improved outcome, both after thrombolytic treatment and after primary PCI[9,31]. However, myocardial tissue perfusion may be impaired despite restoration of normal epicardial blood flow. Recent studies indicate that myocardial perfusion, measured as myocardial TMP grade, may allow further risk stratification. Patients with myocardial TMP grades 0 and 1 have been shown to have larger enzymatic infarct sizes, lower LVEF and higher mortality[6,9,12,13,30,32-35]. Brener et al gave evidence for TMP grade 2 and 3 predicting survival both at 30 days and at three years in a trial with 3,602 patients[14]. In our study, we observed all patients over a period of one year but did not find any difference in clinical outcome between the groups. More patients and a longer follow-up period might have been necessary for this analysis to be conclusive.

Although first-pass perfusion at MRI, measured as maximum contrast enhancement, was significantly reduced in infarcted myocardium compared to remote reference myocardium in both groups, we found no significant differences in first-pass perfusion between patients with TMP grade 0-1 and those with TMP grade 2-3. This is in agreement with our previous results in STEMI patients treated with primary PCI, in which there was a significant reduction in maximum contrast enhancement in the TMP grade 0-1 group on early MRI within five days after the STEMI, but no significant differences after three months[6]. Considering the findings in both of these studies, one could speculate that MRI perfusion might be most useful in the acute phase of myocardial infarction.

Infarct-related artery patency at baseline angiography before primary PCI for STEMI is associated with improved one-year clinical outcomes, including lower death rates[36]. In the present study, when the patients were dichotomised depending on TIMI flow at angiography prior to PCI, no significant differences were found between groups in left ventricular function or infarct size at MRI after three months. However, reduced TIMI flow pre PCI was found to have a significant confounding effect on the predictive effect of TMP grade on infarct size.

We suggest that TMP grading post thrombolysis and PCI may be used as a complementary predictor of large final infarct size and severely reduced LVEF, and may be an alternative when early cardiac magnetic imaging is not available.

Limitations

The generalisation of our data is limited by the small sample size of only 89 patients. The limited number of patients did not allow us to divide TMP grade 2-3 into separate groups with intermediate and normal microcirculation, respectively. Another limitation is that TMP is an angiographic tool which requires specific training before one can draw conclusions on myocardial perfusion.

It should be noted that to define infarct size >17.7% as large was correct for our study population. However, in similar studies of STEMI patients, the 75th percentile for infarct size ranged from 15.7% to 30%. Accordingly, extrapolation of our results to other STEMI populations should be done with caution.

The presence of MVO demonstrated by MRI early after infarction is associated with impaired myocardial salvage[23]. In the present study MVO was not assessed as there were no early MRI data collected.

Conclusions

When assessed by contrast-enhanced MRI three months after STEMI treated by thrombolysis and early PCI, patients with TMP grade 2-3 post PCI had higher LVEF and smaller infarct sizes compared to patients with TMP grade 0-1. The risk of developing large infarctions and low LVEF was significantly increased in patients with TMP grade 0-1, even after adjustment for confounders. TMP grading post thrombolysis and PCI may be used as a predictor of large final infarct size and severely reduced LVEF, and may be an alternative when early cardiac magnetic imaging is not available. TMP grading should be considered as a relevant supplement to TIMI flow when the success of a PCI procedure is evaluated.

Impact on daily practice

When assessed by contrast-enhanced MRI three months after STEMI treated by thrombolysis and early PCI, patients with TMP grade 0-1 post PCI had significantly lower LVEF and larger infarct sizes compared to patients with TMP grade 2-3, even after adjustment for confounders. TMP grading post thrombolysis and PCI may be used as a predictor of large final infarct size and severely reduced LVEF, and may be an alternative when early cardiac magnetic imaging is not available. TMP grading should be considered as a relevant supplement to TIMI flow when the success of a PCI procedure is evaluated.

Acknowledgements

The study was funded by grants from the Scientific Board of the South Eastern Norway Regional Health Authority. The authors are grateful for the excellent MRI scanning assistance

of Vigdis Rosseland and Marianne Nesheim and the secretarial work of Grethe Hansen.

Conflict of interest statement

The authors have no conflicts of interest to declare.

References

1. Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC), Steg PG, James SK, Atar D, Badano LP, Blömstrom-Lundqvist C, Borger MA, Di Mario C, Dickstein K, Ducrocq G, Fernandez-Aviles F, Gershlick AH, Giannuzzi P, Halvorsen S, Huber K, Juni P, Kastrati A, Knuuti J, Lenzen MJ, Mahaffey KW, Valgimigli M, van 't Hof A, Widimsky P, Zahger D. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J.* 2012;33:2569-619.

2. Borgia F, Goodman SG, Halvorsen S, Cantor WJ, Piscione F, Le May MR, Fernandez-Aviles F, Sanchez PL, Dimopoulos K, Scheller B, Armstrong PW, Di Mario C. Early routine percutaneous coronary intervention after fibrinolysis vs. standard therapy in ST-segment elevation myocardial infarction: a meta-analysis. *Eur Heart J.* 2010;31:2156-69.

3. Fernandez-Aviles F, Alonso JJ, Pena G, Blanco J, Alonso-Briales J, Lopez-Mesa J, Fernandez-Vazquez F, Moreu J, Hernandez RA, Castro-Beiras A, Gabriel R, Gibson CM, Sanchez PL; GRACIA-2 (Groupo de Análisis de Cardiopatía Isquémica Aguda) Investigators. Primary angioplasty vs. early routine post-fibrinolysis angioplasty for acute myocardial infarction with ST-segment elevation: the GRACIA-2 non-inferiority, randomized, controlled trial. *Eur Heart J.* 2007;28:949-60.

4. Armstrong PW, Gershlick AH, Goldstein P, Wilcox R, Danays T, Lambert Y, Sulimov V, Rosell Ortiz F, Ostojic M, Welsh RC, Carvalho AC, Nanas J, Arntz HR, Halvorsen S, Huber K, Grajek S, Fresco C, Bluhmki E, Regelin A, Vandenberghe K, Bogaerts K, Van de Werf F; STREAM Investigative Team. Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction. *N Engl J Med.* 2013;368:1379-87.

5. Smith SC Jr, Dove JT, Jacobs AK, Kennedy JW, Kereiakes D, Kern MJ, Kuntz RE, Popma JJ, Schaff HV, Williams DO, Gibbons RJ, Alpert JP, Eagle KA, Faxon DP, Fuster V, Gardner TJ, Gregoratos G, Russell RO, Smith SC Jr; American College of Cardiology/American Heart Association task force on practice guidelines, (Committee to revise the 1993 guidelines for percutaneous transluminal coronary angioplasty); Society for Cardiac Angiography and Interventions. ACC/AHA guidelines for percutaneous coronary intervention (revision of the 1993 PTCA guidelines)-executive summary: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (Committee to revise the 1993 guidelines for percutaneous transluminal coronary angioplasty) endorsed by the Society for Cardiac Angiography and Interventions. *Circulation.* 2001;103: 3019-41.

6. Hoffmann P, Halvorsen S, Stensaeth KH, Brekke M, Muller C, Anker GO, Abdelnoor M, Kløw NE. Myocardial perfusion in ST-elevation myocardial infarction treated successfully with primary angioplasty. *Scand Cardiovasc J.* 2006;40: 96-104.

7. Stone GW, Peterson MA, Lansky AJ, Dangas G, Mehran R, Leon MB. Impact of normalized myocardial perfusion after successful angioplasty in acute myocardial infarction. *J Am Coll Cardiol.* 2002;39:591-7.

8. Suryapranata H, Zijlstra F, MacLeod DC, van den Brand M, de Feyter PJ, Serruys PW. Predictive value of reactive hyperemic response on reperfusion on recovery of regional myocardial function after coronary angioplasty in acute myocardial infarction. *Circulation.* 1994;89:1109-17.

9. Gibson CM, Cannon CP, Murphy SA, Ryan KA, Mesley R, Marble SJ, McCabe CH, Van De Werf F, Braunwald E. Relationship of TIMI myocardial perfusion grade to mortality after administration of thrombolytic drugs. *Circulation.* 2000;101:125-30.

10. van `t Hof AW, Liem A, Suryapranata H, Hoorntje JC, de Boer MJ, Zijlstra F. Angiographic assessment of myocardial reperfusion in patients treated with primary angioplasty for acute myocardial infarction: myocardial blush grade. Zwolle Myocardial Infarction Study Group. *Circulation.* 1998;97:2302-6.

11. Abraham JM, Gibson CM, Pena G, Sanz R, AlMahameed A, Murphy SA, Blanco J, Alonso-Briales J, Lopez-Mesa J, Gimeno F, Sanchez PL, Fernandez-Aviles F; GRACIA-2 (Grupo de Análisis de la Cardiopatía Isquémica Aguda) Investigators. Association of angiographic perfusion score following percutaneous coronary intervention for ST-elevation myocardial infarction with left ventricular remodeling at 6 weeks in GRACIA-2. *J Thromb Thrombolysis.* 2009;27:253-8.

12. Gibson CM, Cannon CP, Murphy SA, Marble SJ, Barron HV, Braunwald E; TIMI Study Group. Relationship of the TIMI myocardial perfusion grades, flow grades, frame count, and percutaneous coronary intervention to long-term outcomes after thrombolytic administration in acute myocardial infarction. *Circulation.* 2002;105:1909-13.

13. Haager PK, Christott P, Heussen N, Lepper W, Hanrath P, Hoffmann R. Prediction of clinical outcome after mechanical revascularization in acute myocardial infarction by markers of myocardial reperfusion. *J Am Coll Cardiol.* 2003;41:532-8.

14. Brener SJ, Cristea E, Mehran R, Dressler O, Lansky AJ, Stone GW. Relationship between angiographic dynamic and densitometric assessment of myocardial reperfusion and survival in patients with acute myocardial infarction treated with primary percutaneous coronary intervention: the harmonizing outcomes with revascularization and stents in AMI (HORIZONS-AMI) trial. *Am Heart J.* 2011;162:1044-51.

15. Wong DT, Leung MC, Richardson JD, Puri R, Bertaso AG, Williams K, Meredith IT, Teo KS, Worthley MI, Worthley SG. Cardiac magnetic resonance derived late microvascular obstruction assessment post ST-segment elevation myocardial infarction is the best predictor of left ventricular function: a comparison of angiographic and cardiac magnetic resonance derived measurements. *Int J Cardiovasc Imaging.* 2012;28:1971-81.

16. Pennell DJ. Cardiovascular magnetic resonance. *Circulation.* 2010;121:692-705.

17. Gerber BL, Garot J, Bluemke DA, Wu KC, Lima JA. Accuracy of contrast-enhanced magnetic resonance imaging in predicting improvement of regional myocardial function in patients after acute myocardial infarction. *Circulation.* 2002;106:1083-9.

18. Kim HW, Farzaneh-Far A, Kim RJ. Cardiovascular magnetic resonance in patients with myocardial infarction: current and emerging applications. *J Am Coll Cardiol.* 2009;55:1-16.

19. Bøhmer E, Arnesen H, Abdelnoor M, Mangschau A, Hoffmann P, Halvorsen S. The NORwegian study on DIstrict treatment of ST-elevation myocardial infarction (NORDISTEMI). *Scand Cardiovasc J.* 2007;41:32-8.

20. Bøhmer E, Hoffmann P, Abdelnoor M, Arnesen H, Halvorsen S. Efficacy and safety of immediate angioplasty versus ischemia-guided management after thrombolysis in acute myocardial infarction in areas with very long transfer distances results of the NORDISTEMI (NORwegian study on DIstrict treatment of ST-elevation myocardial infarction). *J Am Coll Cardiol.* 2010;55:102-10.

21. Sadowski EA, Bennett LK, Chan MR, Wentland AL, Garrett AL, Garrett RW, Djamali A. Nephrogenic systemic fibrosis: risk factors and incidence estimation. *Radiology.* 2007;243:148-57.

22. Wu KC, Zerhouni EA, Judd RM, Lugo-Olivieri CH, Barouch LA, Schulman SP, Blumenthal RS, Lima JA. Prognostic significance of microvascular obstruction by magnetic resonance imaging in patients with acute myocardial infarction. *Circulation.* 1998;97:765-72.

23. Limalanathan S, Eritsland J, Andersen GO, Klow NE, Abdelnoor M, Hoffmann P. Myocardial salvage is reduced in primary PCI-treated STEMI patients with microvascular obstruction, demonstrated by early and late CMR. *PLoS One.* 2013;8:e71780.

24. Mistry N, Beitnes JO, Halvorsen S, Abdelnoor M, Hoffmann P, Kjeldsen SE, Smith G, Aakhus S Bjørnerheim R. Assessment of left ventricular function in ST-elevation myocardial infarction by global longitudinal strain: a comparison with ejection fraction, infarct size, and wall motion score index measured by non-invasive imaging modalities. *Eur J Echocardiogr.* 2011;12:678-83.

25. Andersen GO, Knudsen EC, Aukrust P, Yndestad A, Oie E, Muller C, Seljeflot I, Ueland T. Elevated serum osteoprotegerin levels measured early after acute ST-elevation myocardial infarction predict final infarct size. *Heart.* 2011;97:460-5.

26. Kleinbaum DG, Kupper LL, Morgenstern H. Epidemiologic Research: Principles and Quantitative Methods. New York, NY, USA: John Wiley & Sons Inc; 1982.

27. Niccoli G, Cosentino N, Lombardo A, Sgueglia GA, Spaziani C, Fracassi F, Cataneo L, Minelli S, Burzotta F, Maria Leone A, Porto I, Trani C, Crea F. Angiographic patterns of myocardial reperfusion after primary angioplasty and ventricular remodeling. *Coron Artery Dis.* 2011;22:507-14.

28. Pride YB, Buros JL, Lord E, Southard MC, Harrigan CJ, Ciaglo LN, Sabatine MS, Cannon CP, Gibson CM; TIMI Study Group. Angiographic perfusion score in patients treated with PCI at late angiography following fibrinolytic administration for ST-segment elevation myocardial infarction is associated with morbidity and mortality at 30 days. *J Thromb Thrombolysis.* 2008;26:106-12.

29. Steigen TK, Buller CE, Mancini GB, Jorapur V, Cantor WJ, Rankin JM, Thomas B, Webb JG, Kronsberg SS, Atchison DJ, Lamas GA, Hochman JS, Dzavik V. Myocardial perfusion grade after late infarct artery recanalization is associated with global and regional left ventricular function at one year: analysis from the Total Occlusion Study of Canada-2. *Circ Cardiovasc Interv.* 2010;3:549-55.

30. Zalewski J, Nycz K, Przewlocki T, Durak M, Cul M, Zajdel W, Zmudka K. Evolution of myocardial perfusion during primary angioplasty in spontaneously reperfused infarct-related artery: impact on long-term clinical outcomes and left ventricular function recovery. *Int J Cardiol.* 2011;147:25-31.

31. Hamada S, Nishiue T, Nakamura S, Sugiura T, Kamihata H, Miyoshi H, Imuro Y, Iwasaka T. TIMI frame count immediately after primary coronary angioplasty as a predictor of functional recovery in patients with TIMI 3 reperfused acute myocardial infarction. *J Am Coll Cardiol.* 2001;38:666-71.

32. Appelbaum E, Kirtane AJ, Clark A, Pride YB, Gelfand EV, Harrigan CJ, Kissinger KV, Manning WJ, Gibson CM. Association of TIMI myocardial perfusion grade and ST-segment resolution with cardiovascular magnetic resonance measures of microvascular obstruction and infarct size following ST-segment elevation myocardial infarction. *J Thromb Thrombolysis.* 2009;27:123-9.

33. Marra MP, Corbetti F, Cacciavillani L, Tarantini G, Ramondo AB, Napodano M, Basso C, Lacognata C, Marzari A, Maddalena F, Iliceto S. Relationship between myocardial blush grades, staining, and severe microvascular damage after primary percutaneous coronary intervention a study performed with contrast-enhanced magnetic resonance in a large consecutive series of patients. *Am Heart J.* 2010;159:1124-32.

34. Sorajja P, Gersh BJ, Costantini C, McLaughlin MG, Zimetbaum P, Cox DA, Garcia E, Tcheng JE, Mehran R, Lansky AJ, Kandzari DE, Grines CL, Stone GW. Combined prognostic utility of ST-segment recovery and myocardial blush after primary percutaneous coronary intervention in acute myocardial infarction. *Eur Heart J.* 2005;26:667-74.

35. Henriques JP, Zijlstra F, van 't Hof AW, de Boer MJ, Dambrink JH, Gosselink M, Hoorntje JC, Suryapranata H. Angiographic assessment of reperfusion in acute myocardial infarction by myocardial blush grade. *Circulation.* 2003;107:2115-9.

36. Rakowski T, Dudek D, Dziewierz A, Yu J, Witzenbichler B, Guagliumi G, Kornowski R, Hartmann F, Lansky AJ, Brener SJ, Mehran R, Stone GW. Impact of infarct-related artery patency before primary PCI on outcome in patients with ST-segment elevation myocardial infarction: the HORIZONS-AMI trial. *EuroIntervention.* 2013;8:1307-14.