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Is the myocardial blush grade scored by the operator during primary percutaneous coronary intervention of prognostic value in ST-elevation myocardial infarction patients in routine clinical practice?
Abstract

Background
Multiple trials have documented that myocardial blush grade (MBG) after primary percutaneous coronary intervention (PCI) for ST-elevation myocardial infarction (STEMI) has prognostic value for long-term clinical outcome. However, to the best of our knowledge, no study has determined the clinical use of MBG in routine clinical practice. We determined the prognostic value of MBG scored by the operator during primary PCI in consecutive patients with STEMI.

Methods and results
The prognostic value of MBG scored by the operator in relation to 1-year all cause mortality was evaluated in all patients with STEMI who underwent primary PCI between January 2004 and July 2008 in our hospital. The incidence of MBG 0, 1, 2, and 3 was 12%, 14%, 36%, and 38%, respectively, in 2118 consecutive patients with STEMI. Follow-up of all 2118 patients showed a 1-year all cause mortality rate of 8% (168 of 2118): 24%, 10%, 6%, and 4%, respectively, among patients with MBG 0, 1, 2, and 3 (p<0.001). In the 1763 patients with Thrombolysis in Myocardial Infarction (TIMI) flow grade 3 after PCI, these mortality rates were 17%, 10%, 6%, and 4%, respectively (p<0.001). MBG scored by the operator was a strong independent predictor of 1-year all cause mortality corrected for other well-known predictive variables, including TIMI flow grade.

Conclusions
MBG scored by the operator during primary PCI has prognostic value for 1-year all cause mortality in patients with STEMI in routine clinical practice. Therefore, the MBG should be documented, in addition to the TIMI flow grade, during primary PCI in patients with STEMI in standard PCI reports in routine clinical practice.
Introduction

Depending on the duration of coronary occlusion, myocardial infarction leads to necrosis of myocytes and eventually to destruction of the microvascular bed. The primary goal of primary percutaneous coronary intervention (PCI) for ST-elevation myocardial infarction (STEMI) is restoration of epicardial blood flow to provide perfusion into the infarcted part of the myocardium. The rate of restoration of epicardial blood flow after PCI can be assessed by the angiographic Thrombolysis in Myocardial Infarction (TIMI) flow grade. TIMI flow grade is associated with clinical outcome. In ≈90% of the patients with STEMI, restored epicardial blood flow, defined as TIMI flow grade 3, is achieved after primary PCI. However, despite restored epicardial blood flow, a substantial percentage of patients have signs of impaired myocardial reperfusion and therefore have an impaired prognosis.

Myocardial blush grade (MBG) is a simple visual angiographic assessment of myocardial perfusion in the infarct area, as first described by van’t Hof et al; MBG seems to be of additional value, especially in patients with restored epicardial blood flow because MBG reflects the extent of damage of the microvascular bed. In several studies, the MBG is associated with ST-segment elevation resolution, enzymatic infarct size, left ventricular function, and long-term mortality. Therefore, MBG is often used as an end point in clinical trials. In routine clinical practice, MBG is not often used as a prognostic tool, possibly because of concerns that the subjectivity of the operator will limit its prognostic value. Until now, no studies have validated the prognostic value of MBG scored by the operator during primary PCI in routine clinical practice, but they have relied on independent core laboratory or experienced observers blinded to all clinical data. In this study, we evaluated the relation between MBG scored by the operator during primary PCI and 1-year all cause mortality in patients with STEMI and its additional prognostic value when TIMI flow grade 3 is achieved after primary PCI.

Methods

Patient population
In this “real-world” analysis, all consecutive patients with STEMI were included who were treated with primary PCI from January 2004 to July 2008 in our hospital. During this period, 1599 patients with STEMI were included in 1 of our randomized controlled trials. Our trials include TAPAS (Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study; n=1071), Diver versus Export (n=80), and ADAPT (ADenosine Administration during and after Primary percutaneous coronary intervention in acute myocardial infarction; n=448). These trials included patients with suspected STEMI
in the period between January 2005 and July 2008. Trial exclusion criteria were rescue PCI after thrombolysis, cardiogenic shock, known disease with a life expectancy of <6 months, and lack of informed consent. For this study, no exclusion criteria were used, and all patients with STEMI included in our trials (trial patients) and all patients with STEMI not included in our trials (nontrial patients) were analyzed.

Treatment
From January 2004 to January 2005, patients with STEMI were treated with conventional PCI (balloon angioplasty followed by stent implantation). From January 2005 to December 2006, conventional PCI and thrombus aspiration followed by stent implantation were randomly performed in context of the TAPAS trial. Thrombus aspiration became the preferred treatment since December 2006. Most patients received bare-metal stents. Acute pharmacotherapy was according to current international guidelines, including aspirin, clopidogrel, and the glycoprotein IIb/IIa inhibitor abciximab. Maintenance pharmacotherapy consisted of aspirin, clopidogrel for at least 1 month, β-blockers, lipid-lowering agents, and angiotensin-converting enzyme inhibitors or angiotensin-II receptor blockers.

Angiographic analysis
The operators scored the TIMI flow grades (operator TIMI flow grade) and MBG (operator MBG) during the PCI procedure and registered the outcome in the catheterization laboratory database. In all patients, TIMI flow grade was scored before PCI, and TIMI flow grade and MBG were scored after PCI after intracoronary nitroglycerin was administered. In the trial patients, an independent core laboratory or 2 experienced observers blinded to all clinical data scored TIMI flow grades (core laboratory TIMI flow grade) and MBG (core laboratory MBG) on recorded angiograms, as previously described.

End points and definitions
TIMI flow grade was classified as 0: no antegrade flow, 1: minimal antegrade flow into the obstructed segment, 2: slow antegrade flow into the distal bed, and 3: normal antegrade flow into the distal bed. The MBG was determined by the contrast density in an angiographic projection that isolated the distal myocardial region of the infarct-related artery. Detailed description of the angiographic requirements to assess the MBG has been published previously by van’t Hof et al; MBG of the myocardial infarct region was classified as 0: no myocardial blush, 1: minimal myocardial blush, 2: moderate myocardial blush, or 3: normal myocardial blush, all compared with the MBG of myocardial regions of noninfarct-related arteries. Persisting myocardial blush was also graded as 0 because this is considered to be extravasation of angiographic contrast medium associated with hemorrhage. Enzymatic
Myocardial Blush Grade scored by the operator

Infarct size was determined as peak creatinine kinase. All cause 1-year mortality was collected using municipal civil registries. Because only patients who are lost to follow-up by municipal civil registries could not be tracked, this system provides completeness of follow-up with regard to vital status in >99% of patients admitted to our department.

### Statistical analysis

Normally distributed continuous variables are presented as mean±SD and were compared using a 2-tailed Student t test. Skewed distributed continuous variables are presented as median with interquartile range and were compared using a Mann-Whitney U test. Categorical variables are presented as number and percentage and were compared using the χ² test or Fisher exact test. To determine the agreement between operators and core laboratory scoring, unweighted kappa was used with TIMI flow grades and MBG grouped as 0 or 1 versus 2 or 3. The additional predictive value for 1-year all cause mortality by operator MBG compared with the often used prognostic scores during the procedure, TIMI flow grade before and after PCI, was evaluated by receiver operating characteristic curves. Logistic regression analysis for mortality was performed using well-known prognostic variables: age, anterior infarction, peak creatinine kinase, TIMI flow grade before and after PCI, and MBG. A large enzymatic infarct size was defined as creatinine kinase peak at least 15 times the upper limit of the normal values. Independent predictors of 1-year all cause mortality were identified using the backward stepwise regression. Statistical significance was defined as a 2-sided p-value of <0.05. Statistical analysis was performed using SPSS software version 16.0 (SPSS Inc, Chicago, Ill).
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Results

Study population
A total of 2375 patients with STEMI underwent primary PCI in our hospital in the 4.6-year period (Figure 1). In 89% (2118 of 2375) of the patients, immediate TIMI flow grades and MBG were scored by the operator. In trial patients, TIMI flow grades and MBG were scored in 86% (1375 of 1599) by operator as well as by core laboratory. In nontrial patients, TIMI flow grades and MBG were scored in 96% (743 of 776) by operator. Compared with trial patients, nontrial patients had worse angiographic characteristics and a higher 1-year all cause mortality rate (Table 1). In all consecutive patients with STEMI, operator TIMI flow grade 3 and operator MBG 3 after PCI were achieved in 83% and 38%, and operator TIMI flow grade 0 and operator MBG 0 after PCI were scored in 2% and 12% of the patients. In trial patients, operator TIMI flow grade 3 and operator MBG 3 after PCI were achieved in 85% and 40%, and operator TIMI flow grade 0 and operator MBG 0 after PCI were scored in 1% and 5% of the patients. In nontrial patients, operator TIMI flow grade 3 and operator MBG 3 after PCI were achieved in 80% and 35%, and operator TIMI flow grade 0 and operator MBG 0 after PCI were scored in 4% and 24% of the patients. One-year all cause mortality was 8% (168 of 2118) in all consecutive patients with STEMI, 4% (53 of 1375) in the trial patients, and 16% (115 of 743) in the nontrial patients.

Agreement between operator and core laboratory scoring of MBG and TIMI flow grade
The incidence of the overall scored grades of myocardial blush between operators and core laboratory in trial patients is compatible (Figure 2). The highest agreement between operators and core laboratory was in TIMI flow grade before PCI (kappa 0.81) compared with TIMI flow grade after PCI (kappa 0.62) and MBG (kappa 0.47), when grouped in 0 or 1 versus 2 or 3. The kappa was lower for TIMI flow grade after PCI because of the high incidence of grade 2 and 3 after PCI (Figure 3).

Prognostic value of MBG scored by the operator
There were strong relations among operator TIMI flow grade before PCI (p=0.006), operator TIMI flow grade after PCI (p<0.001), operator MBG (p<0.001), and 1-year all cause mortality in all consecutive patients with STEMI (Figure 4). Per grade of myocardial blush, the prognosis decreased with a markedly poor prognosis for operator MBG 0 (Figure 5). Compared with
# Myocardial Blush Grade scored by the operator

## General characteristics

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## Angiographic characteristics

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Data are presented as mean±SD, median (IQR) or as number (%).
P-value represents the difference between trial patients and nontrial patients. Ischemic time was recorded in 1866 consecutive STEMI patients, in 1282 trial patients and in 584 nontrial patients.

Figure 2 | Angiographic MBG scored by operator and core laboratory in the trial patients (n=1375)

Figure 3 | Agreement of TIMI flow grade and MBG between operators and core laboratory in the trial patients (n=1375)
operator MBG, the relation between core laboratory MBG and mortality was similar (core laboratory MBG 0, 1, 2, 3: 15.3%, 4.6%, 2.8%, 2.9%, respectively; p<0.001). In nontrial patients alone, a similar and significant relation between operator MBG and mortality was found.

In the 83% of patients with operator TIMI flow grade 3 after PCI, operator MBG was 0 in 7%, 1 in 11%, 2 in 37%, and 3 in 45% of the patients. In these patients with restored epicardial flow after PCI, operator MBG remained a strong predictor for mortality (Figure 6). Operator MBG 0 or 1 was seen more often in anterior infarction (p<0.001), even when operator TIMI flow grade 3 was achieved by PCI (p<0.001). The receiver operating characteristic analysis showed that operator MBG had additional predictive value for 1-year all cause mortality compared with TIMI flow grade before and after PCI (Figure 7). Multivariable analysis showed that operator MBG is a strong and independent predictor of 1-year all cause mortality corrected for age, anterior infarction, enzymatic infarct size, and TIMI flow grade before and after PCI (Table 2).

Discussion

In this real-world study, we show that MBG scored by the operator during the PCI procedure, as a determinant of myocardial reperfusion, is a strong predictor of long-term mortality in patients with STEMI treated with primary PCI. After correction for other predictive variables (age, anterior infarction, enzymatic infarct size, and TIMI flow grade before and after PCI), MBG remains an independent prognostic variable (odds ratio of MBG 0 or 1 versus 2 or 3: 2.75; 95% CI: 1.95 to 3.86; p<0.001) Moreover, in patients with restored epicardial blood flow after primary PCI, operator MBG has additional prognostic value.

Restoration of the epicardial blood flow to provide myocardial reperfusion has been the target for treatment of patients with myocardial infarction for many years.2,3 With primary PCI, a restored epicardial blood flow is achieved in ≈90% of the patients in several trials.7,8,19,20 The prognostic value of epicardial blood flow, classified as TIMI flow grade, is well known.4,5 Our study also shows that operator TIMI flow grade before and after PCI are predictors of long-term mortality in routine clinical practice. However, TIMI flow grade does not describe the reperfusion of the infarcted myocardium. Van’t Hof et al described MBG as a visual assessment of angiographic contrast density in the myocardial region of the infarct-related artery as a reflection of myocardial reperfusion. Several trials have shown the prognostic value of retrospective scored MBG by experienced observers or independent core laboratory blinded to all clinical data.6,7,11,12,19 To the best of our knowledge, this study is the first that uses MBG obtained during the PCI procedure in routine clinical practice. We show that operator MBG is a predictor of long-term mortality in patients with STEMI
treated with primary PCI. Furthermore, this study had the capacity to identify progressively decreasing prognosis per grade of myocardial blush, with a markedly poor prognosis in MBG 0.

That the restored epicardial blood flow is not identical to restored myocardial perfusion can be explained as follows. Myocardial perfusion is related to the extent of myocardial necrosis caused by microvascular dysfunction. This depends partly on the duration of coronary artery occlusion, the size of the myocardium supplied by the infarct-related artery, and the quality of collateral circulation. However, besides disturbed reperfusion by epicardial or collateral vessels, the impaired microvascular perfusion can also be caused by edema, inflammation, neurohormonal reflexes, vasoconstriction, and spontaneous or PCI-induced distal atherothrombotic embolization. In 11% to 50% of the patients with STEMI no or reduced myocardial perfusion (“no reflow”) is observed after PCI, despite restored epicardial blood flow. This impaired myocardial perfusion is
associated with decreased clinical outcomes, and therefore, restored epicardial blood flow is no guarantee for restored myocardial viability and clinical outcome. In our study, 18% had impaired myocardial blush despite TIMI flow grade 3 after PCI. In these patients with MBG 0 or 1, a mortality rate of 17% and 10% was observed compared with a mortality rate of 6% and 4% when MBG 2 or 3 was achieved (p<0.001). In the receiver operating characteristic analysis, the predictability of 1-year mortality increased using MBG beyond the TIMI flow grade before and after PCI. Furthermore, in multivariable analysis, MBG remained an independent predictor after adjustment for other known prognostic variables, including TIMI flow grade after PCI. Therefore, MBG identifies an additional patient population at risk on top of TIMI flow grade. This implicates that documentation of MBG has prognostic value in routine clinical practice, in particular when TIMI flow grade 3 is achieved after PCI.

As is the case for TIMI flow grade, MBG is a subjective angiographic parameter. In the trial patients, the incidence of the different grades of myocardial blush was comparable between operators and core laboratory. The agreement between operators and core laboratory seemed to be lower in MBG compared with TIMI flow grade after PCI. It is important to realize that the core laboratory analyzed coronary angiograms blinded to all
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Figure 6 | Relation between 1-year mortality and operator MBG in consecutive patients with STEMI with TIMI 3 post-PCI (n=1763)

![Graph showing 1-year all cause mortality (%) vs. Myocardial blush grade.](image)

Figure 7 | Additional predictive value of operator MBG compared to TIMI flow grade before and after PCI (n=2118)

![Graph showing Receiver operating characteristic curve for TIMI flow grade before and after PCI (area under the curve of 0.62) compared to the curve with additional operator MBG (area under the curve of 0.68). The value per score of TIMI flow or MBG was determined by its regression coefficient.](image)
Myocardial Blush Grade scored by the operator

clinical data, whereas operators will have been influenced by the clinical presentation of the patients. Furthermore, the scoring during night hours by the operator may be less accurate. Experience and feedback in this relative new angiographic assessment may reduce variability. Furthermore, STEMI trials report variable incidences of the different grades of myocardial blush scored by core laboratory (Table 3). Still, both our study and these trials show that in different centers, distinguishing MBG 0 and 1 from 2 and 3 has major prognostic implications. Other techniques are available that assess myocardial perfusion in a more quantitative manner. Most studies have been performed with myocardial contrast echocardiography. Decreased myocardial perfusion determined by myocardial contrast echocardiography is associated with left ventricular remodeling, heart failure, and cardiac mortality. High-contrast MRI measures microvascular obstruction and myocardial damage and may become the preferred technique. Effective myocardial reperfusion may gradually occur in the first 10 days after STEMI, which is the advantage of these techniques that are mostly performed after this period. Quantitative Blush Evaluator is a computer-assisted assessment of myocardial perfusion that is correlated with core laboratory MBG and is a predictor of long-term mortality. The advantage of using angiographic MBG is that it is a readily available and simple method that can be used to estimate the myocardial reperfusion immediately after PCI without the need for additional diagnostic procedures with issues of availability and expertise.

This study included all trial and nontrial patients with STEMI in a 4.6-year period. The incidence of MBG 0 and 1 differed between trial patients (5% and 15%) and nontrial patients (24% and 12%). The nontrial cohort were patients who underwent primary PCI when no trials were performed, mainly in 2004 or between 2 trials (65% 486 of 743) and

Table 2 | Odds ratio for 1-year mortality including operator MBG in all consecutive STEMI patients (n=2118)

<table>
<thead>
<tr>
<th></th>
<th>Univariate analysis</th>
<th>Multivariable analysis</th>
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<tbody>
<tr>
<td></td>
<td>Odds ratio 95% CI</td>
<td>p-value</td>
</tr>
<tr>
<td>Age, years</td>
<td>1.05 (1.04-1.07)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anterior infarction</td>
<td>1.46 (1.07-2.01)</td>
<td>0.018</td>
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<tr>
<td>Creatinine Kinase peak &gt;1500U/L</td>
<td>1.69 (1.21-2.36)</td>
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<td>TIMI pre-PCI 0 or 1</td>
<td>1.90 (1.30-2.80)</td>
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<td>TIMI post-PCI &lt;3</td>
<td>2.43 (1.71-3.44)</td>
<td>&lt;0.001</td>
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<td>MBG 0 or 1</td>
<td>3.71 (2.69-5.12)</td>
<td>&lt;0.001</td>
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TIMI pre-PCI 0 or 1 was compared to TIMI pre-PCI 2 or 3; TIMI post-PCI <3 was compared to TIMI post-PCI 3; MBG 0 or 1 was compared to MBG 2 or 3. During multivariable regression analysis the following variables were subsequently dropped as significant predictors for 1-year all cause mortality: TIMI post-PCI <3, anterior infarction, and TIMI pre-PCI 0 or 1.
patients who were excluded from our trials (35% 257 of 743). In 54 patients, the operator excluded the patient from a trial because of cardiogenic shock. This also explains the higher mortality rate in nontrial patients. In most trials where MBG was assessed, cardiogenic shock patients were excluded. These patients are most likely to have a poor MBG. Tarantini et al\textsuperscript{28} described an incidence of MBG 0 or 1 of 66% in patients with cardiogenic shock after primary PCI with a mortality rate of 81%. Another explanation for the poorer outcome of the nontrial patients is that glycoprotein IIb/IIIa receptor antagonists were less administered in the nontrial patients compared with the trial patients (69% versus 93%). It is known that glycoprotein IIb/IIIa reduces mortality.\textsuperscript{29} Irrespective of these differences between trial and nontrial patients, there remained a strong relation between MBG and long-term mortality.

**Limitations**

TIMI flow grade and MBG were not scored by operator, core laboratory, or both in all patients. Scoring MBG is dependent on a specific and prolonged angiographic projection while the patient is holding his or her breath. More effort by the operator will increase the number of adequate angiograms. Still, assessable angiograms were present in 89% of all consecutive patients with STEMI.

**Conclusions and implications**

Angiographic MBG scored by the operator during primary PCI in patients with STEMI is an independent predictor for 1-year all cause mortality in routine clinical practice. Even when TIMI flow grade 3 is achieved after PCI, operator MBG has an additional predictive value. Furthermore, probably, this is the first study that could categorize MBG in 4 groups.
Myocardial Blush Grade scored by the operator

with decreasing prognosis per grade, with a markedly poor prognosis in MBG 0. Compared with other functional outcome parameters, such as in MRI and echocardiography, the operator-scored MBG has the important practical advantage that it is assessed directly after the primary PCI procedure. This all implicates that MBG scored by the operator during primary PCI can be used to improve early risk stratification in patients with STEMI with the opportunity to intensify the treatment for high-risk patients. We are eagerly awaiting the results of trials studying various additional interventions to improve left ventricular function when the myocardial perfusion is not restored after PCI.30–33
References


