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# Angiographic predictors of outcome in myocardial infarction patients presenting with cardiogenic shock: a CULPRIT-SHOCK angiographic substudy

**Pavel Overtchouk**[1,2,3], MD; Olivier Barthélémy[2], MD; Marie Hauguel-Moreau[2], MD; Paul Guedeney[2], MD; Stéphanie Rouanet[4], MD; Michel Zeitouni[2], MD; Johanne Silvain[2], MD; Jean-Philippe Collet[2], MD; Eric Vicaut[5], MD; Uwe Zeymer[6], MD; Steffen Desch[7], MD; Holger Thiele[7], MD; Gilles Montalescot[2]*, MD; for the CULPRIT-SHOCK investigators

*1. Alviss.ai - Read Better, Paris, France; 2. Sorbonne Université, ACTION Study Group, INSERM UMRS_1166, Institut de Cardiologie (AP-HP), Paris, France; 3. Department of Cardiology, University Hospital of Bern, Bern, Switzerland; 4. Statistician Unit, StatEthic, Levallois-Perret, France; 5. ACTION Study Group, Unité de Recherche Clinique, Hôpital Lariboisière (AP-HP), Paris, France; 6. Heart Centre Ludwigshafen, Department of Cardiology, Ludwigshafen, Germany; 7. Heart Center Leipzig at University of Leipzig and Leipzig Heart Institute, Leipzig, Germany*

*H. Thiele and G. Montalescot should both be considered as senior authors.*

*A list of study collaborators can be found in the Appendix paragraph.*

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**KEYWORDS**

- ACS/NSTE-ACS
- cardiogenic shock
- STEMI

## Abstract

**Aims:** The aim of this study was to determine the prognostic impact of pre- and post-PCI TIMI flow grade and TIMI myocardial perfusion grade (TMPG) in a well-defined group of patients with cardiogenic shock due to acute myocardial infarction.

**Methods and results:** Patients with infarct-related cardiogenic shock randomised into the CULPRIT-SHOCK trial were included in the angiographic predictor analysis whenever their TIMI flow grade or TMPG was available in the core lab database (96.9% of cases). A multivariable logistic regression analysis, adjusted on non-angiographic covariates, was performed to investigate whether TIMI flow grade or TMPG was independently associated with all-cause mortality or renal replacement therapy up to one year. Pre-PCI TIMI flow grade and TMPG did not impact on mortality. When analysed in separate multivariable models, post-PCI TIMI 3 flow and TMPG grade 3 were both significantly associated with reduced risk of 30-day mortality: aOR 0.61 (95% CI: 0.38-0.97, p=0.037) and 0.46 (95% CI: 0.29-0.72, p<0.001), respectively. When considered in the same multivariable model, only TMPG was significantly associated with 30-day mortality (aOR 0.38 [0.20-0.71], p=0.002), the 30-day composite of all-cause mortality and renal replacement therapy (aOR 0.34 [0.18-0.66], p=0.001) and mortality at one-year follow-up (aOR 0.46 [0.24-0.88], p=0.02).

**Conclusions:** Post-PCI TIMI flow grade and TMPG are associated with mortality after PCI. TMPG is a better discriminator, supporting microcirculation rather than epicardial reperfusion for prognosis estimation.

**Corresponding author: ACTION Study Group, Institut de Cardiologie, Hôpital Pitié-Salpêtrière, 47-83 bld de l'Hôpital, 75013 Paris, France. E-mail: gilles.montalescot@aphp.fr*



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## Abbreviations

| | |
|---|---|
| **aOR** | adjusted odds ratio |
| **OR** | odds ratio |
| **PCI** | percutaneous coronary intervention |
| **RRT** | renal replacement therapy |
| **TIMI** | Thrombolysis In Myocardial Infarction |
| **TMPG** | TIMI myocardial perfusion grade |

## Introduction

Percutaneous coronary intervention (PCI) reduces mortality in patients presenting with acute myocardial infarction (MI)[1,2] irrespective of the presence of cardiogenic shock[3]. However, the estimation of the efficacy of percutaneous revascularisation can be further stratified by angiographic measures such as Thrombolysis In Myocardial Infarction (TIMI) flow grade, TIMI myocardial perfusion grade (TMPG) or myocardial blush grade as well as by TIMI frame count (TFC). Indeed, TIMI flow grade, TMPG and TFC have been proven to be associated with mortality in patients with MI predominantly without cardiogenic shock and have therefore been used to define the success of revascularisation[4-7]. Nevertheless, evidence concerning these parameters in patients with cardiogenic shock is scarce[8,9], and systemic microcirculation and macrocirculation might be more relevant than myocardial reperfusion. The CULPRIT-SHOCK trial demonstrated that percutaneous revascularisation of the culprit coronary artery only was superior to an immediate multivessel PCI in patients with acute MI with multiple vessel coronary artery disease (CAD) and cardiogenic shock[10].

We sought to determine whether angiographic revascularisation indicators (TIMI flow grade, TMPG), blindly evaluated in an angiographic core laboratory, are associated with outcome after PCI in a well-defined cohort of cardiogenic shock patients with acute MI and multivessel CAD.

**Editorial, see page 1209**

## Methods

### STUDY POPULATION

The CULPRIT-SHOCK randomised, open-label, multicentre trial demonstrated the superiority of culprit lesion-only PCI with possible staged revascularisation over an immediate multivessel PCI strategy in patients with cardiogenic shock related to MI, regarding all-cause mortality or renal replacement therapy (RRT) at 30 days and one year[10,11]. Patients included in the CULPRIT-SHOCK trial had a core lab angiographic blinded evaluation of their coronary angiograms. We analysed all patients with reported data on pre-PCI TIMI flow grade or TMPG and considered pre- and post-PCI TIMI flow grade and TMPG of the culprit artery only.

### ANGIOGRAPHIC CORE LABORATORY

The ACTION (Allies in Cardiovascular Trials, Initiatives and Organized Networks) angiographic core laboratory (Institut de Cardiologie, Pitié-Salpêtrière Hospital) was blinded to patient characteristics, outcomes and randomisation group. For each patient, two blinded readers adjudicated the angiographic parameters (TIMI flow grade, TMPG) of the culprit artery, as previously described[12].

TIMI flow grade and TMPG are complementary angiographic measurements representative of coronary circulation. TIMI flow grade evaluates the quality of coronary flow in epicardial vessels by measuring coronary artery clearance of radiographic dye. TMPG evaluates the quality of coronary flow in the myocardial microvasculature. TIMI flow grade and TMPG were recorded in accordance with their original definitions[4,12,13] **(Supplementary Table 1, Supplementary Figure 1)**.

All data were entered into a dedicated computerised database. In case of disagreement between readers, a third and eventually a fourth independent reader were requested to reach a consensus. For the purposes of this study, angiographic parameters were dichotomised into TIMI flow grade <3 versus TIMI flow grade 3 and TMPG <3 versus TMPG 3.

### OBJECTIVE AND OUTCOMES

We hypothesised that the angiographic measures used in clinical practice for estimation of the efficacy of percutaneous revascularisation are associated with prognosis after PCI for acute MI complicated by cardiogenic shock. In addition, we hypothesised that their relative importance would differ.

The objective was to determine whether TIMI flow grade and TMPG (3 versus <3 for both parameters) before and after PCI are associated with short- and long-term outcomes. Outcomes of interest for this substudy were all-cause mortality at 30 days, all-cause death or renal replacement therapy at 30 days, and all-cause mortality at one-year follow-up. Recurrent MI and rehospitalisation for heart failure at 30 days were also considered.

### STATISTICAL ANALYSIS

Continuous variables are reported as mean±standard deviation (SD). Categorical variables are reported as number (%). To investigate the association between angiographic parameters and outcomes, we evaluated TIMI flow grade and TMPG (3 versus <3 for both parameters) as separate and dependent variables in different multivariable models. Multivariate logistic regression models were used to evaluate the independent association between TIMI flow grade or TMPG and outcomes. In each model, TIMI flow grade or TMPG was adjusted for baseline clinical and procedural characteristics significantly associated with outcomes on univariate analysis ($p<0.2$). To investigate which angiographic parameter would be the most clinically relevant, we also built a multivariable model including both TIMI flow grade and TMPG. The list of covariables is as follows: age, gender, body mass index, current smoking, hypercholesterolaemia, diabetes mellitus, chronic renal failure, previous PCI, previous stroke, previous coronary artery bypass grafting (CABG), arterial lactate >2 mmol/l, fibrinolysis before randomisation, left main or left anterior descending (LAD) culprit artery, ≥1 chronic total occlusion, femoral access, stent implantation in culprit artery, randomisation group, mechanical circulatory support, mechanical ventilation, and catecholamine therapy.

The main analyses were performed entering randomisation group as a covariable. However, in the CULPRIT-SHOCK trial the crossover rate was approximatively 10%. Hence, sensitivity analyses were performed entering the type of revascularisation procedure (culprit only versus multiple vessel PCI) instead of randomisation group as a covariable in the multivariable analysis ("as-treated" analysis) to investigate the possible impact of crossovers and type of revascularisation on outcomes.

Results are reported as adjusted odds ratios (aOR) with their 95% confidence intervals (95% CI). A p-value <0.05 was considered significant. All statistical analyses were performed with SAS statistical software, release 9.4 (SAS Institute Inc., Cary, NC, USA).

## Results

Out of the 686 patients included in the CULPRIT-SHOCK trial, 665 (96.9%) were included in the angiographic substudy. Mean patient age was 68.5±11.4 years, one third had diabetes mellitus and 24% were female. Two thirds of the patients presented with ST-segment elevation myocardial infarction (STEMI), most had triple-vessel disease (64%) and the LAD was the most frequent culprit artery (42%). Severe cardiogenic shock was common, as attested by catecholamine use in 90% of patients and mechanical circulatory support in 29% of patients. All-cause mortality was 47% and 53% at 30 days and one year, respectively **(Table 1, Table 2)**.

### TIMI FLOW GRADE AND TMPG

As per the angiographic core lab, for the culprit artery TIMI flow grade and TMPG before PCI were available in 663 (99.7%) and 598 (89.9%) patients, whereas TIMI flow grade and TMPG post PCI were available in 639 (96.1%) and 504 (75.8%) patients, respectively. The incompleteness of core lab angiographic data is due mainly to the limited availability or inadequate quality of the angiographic films. Before PCI, the number of patients with TMPG 3 and TIMI flow grade <3 was 44 (19.4%), almost exclusively represented by patients with TIMI flow 2. Before PCI, the number of patients with TIMI flow grade 3 and TMPG <3 was 12 (3.2%). Before PCI, TIMI flow grade was 3 in 220 (33.2%) patients and TMPG was 3 in 228 (38.1%) patients. Post PCI, TIMI flow grade 3 was achieved in 499 (78.1%) patients and TMPG 3 in 320 (63.5%) patients. The comparison of effects of the different grades of post-PCI TIMI flow grade and TMPG on 30-day mortality, 30-day mortality or RRT, and one-year mortality displayed an apparently stepwise relationship **(Table 3, Table 4, Figure 1-Figure 3)**. The multivariable analysis including both post-PCI TIMI flow grade and TMPG included 463, 449 and 464 patients for the endpoints 30-day mortality, 30-day mortality or RRT, and one-year mortality, respectively.

### ANGIOGRAPHIC PARAMETERS AND 30-DAY ALL-CAUSE MORTALITY

Neither TIMI flow grade nor TMPG pre-PCI was associated with 30-day mortality after univariate analysis (p=0.56 and 0.11, respectively). Both TIMI flow grade and TMPG (3 versus <3 for both parameters) in the culprit artery after PCI were associated with 30-day mortality in univariate analysis (p<0.001). TIMI flow 3 and TMPG 3 both remained significantly associated with lower

**Table 1. Patient characteristics.**

| | |
|---|---|
| **Clinical characteristics** | |
| Age, years | 68.5±11.4 |
| Female | 156 (23.5%) |
| Body mass index, kg/m² | 27.3±4.2 |
| **Risk factors** | |
| Active smoking | 171/640 (26.7%) |
| Hypertension | 393/653 (60.2%) |
| Hypercholesterolaemia | 222/650 (34.2%) |
| Diabetes mellitus | 209/651 (32.1%) |
| **Past medical history** | |
| Previous myocardial infarction | 109/653 (16.7%) |
| Previous stroke | 47/656 (7.2%) |
| Peripheral artery disease | 78/657 (11.9%) |
| Previous percutaneous coronary intervention | 123/653 (18.8%) |
| Previous coronary artery bypass graft | 33/657 (5.0%) |
| **Presentation** | |
| Fibrinolysis <24 hours before randomisation | 32/662 (4.8%) |
| Resuscitation before randomisation | 354/663 (53.4%) |
| ST-segment elevation myocardial infarction | 405/645 (62.8%) |
| **Number of affected vessels** | |
| Single-vessel disease | 5 (0.8%) |
| Two-vessel disease | 238 (35.8%) |
| Triple-vessel disease | 422 (63.5%) |
| **Culprit vessel (core lab)** | |
| Left main coronary artery | 60 (9.0%) |
| Left anterior descending artery | 277 (41.7%) |
| Circumflex artery | 140 (21.1%) |
| Right coronary artery | 181 (27.2%) |
| Bypass graft | 7 (1.1%) |
| Chronic total occlusion (core lab) | 157 (23.6%) |
| Data are expressed as mean±SD, or number (%). | |

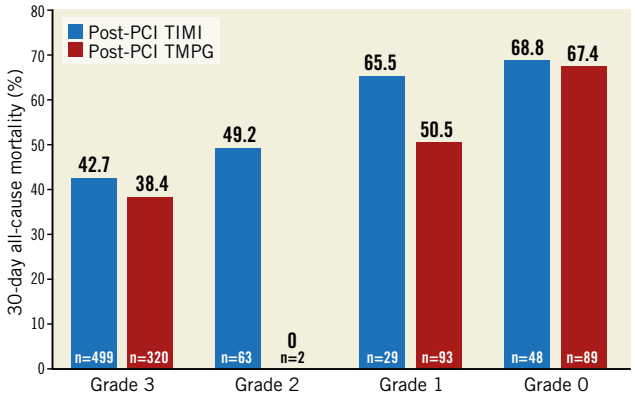


**Figure 1.** *Proportions of 30-day all-cause mortality according to post-PCI TIMI flow grade or TMPG.*

**Table 2. Procedural characteristics and outcomes.**

| | |
|---|---|
| **Procedural characteristics** | |
| Femoral arterial access | 548 (82.4%) |
| Drug-eluting stent in culprit artery | 594/631 (94.1%) |
| Thromboaspiration | 97 (14.6%) |
| **Acute management** | |
| Mechanical circulatory support | 191 (28.7%) |
| Intra-aortic balloon pump | 49 (7.4%) |
| Impella (2.5, CP) | 82 (12.3%) |
| TandemHeart | 2 (0.3%) |
| Extracorporeal membrane oxygenation | 45 (6.8%) |
| Other | 19 (2.9%) |
| Mild hypothermia | 220/663 (33.2%) |
| Mechanical ventilation | 538/662 (81.3%) |
| Catecholamine use | 597/662 (90.2%) |
| Aspirin* | 484/664 (73.2%) |
| Clopidogrel* | 121/664 (18.2%) |
| Prasugrel* | 88/664 (13.3%) |
| Ticagrelor* | 154/664 (23.2%) |
| Glycoprotein IIb/IIIa inhibitor* | 143/664 (21.5%) |
| Cangrelor* | 16/664 (2.4%) |
| Unfractionated heparin* | 539/664 (81.2%) |
| Low molecular weight heparin* | 96/664 (14.5%) |
| Bivalirudin* | 39/664 (5.9%) |
| **Outcomes** | |
| 30-day all-cause mortality | 313 (47.1) |
| 30-day all-cause mortality or renal replacement therapy | 335 (50.4) |
| 1-year mortality | 354 (53.2) |

Data are expressed as mean±SD, or number (%). *Antiplatelet and anticoagulant drugs administered in the catheterisation laboratory.

risk of 30-day mortality after adjustment for other non-angiographic covariates in respective multivariable models, with an aOR of 0.61 (95% CI: 0.38-0.97), p=0.037 for TIMI flow grade,

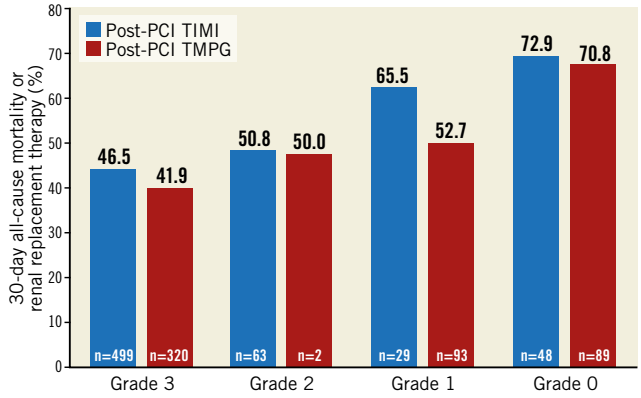


**Figure 2.** *Proportions of 30-day all-cause-mortality and renal replacement therapy according to post-PCI TIMI flow grade or TMPG.*

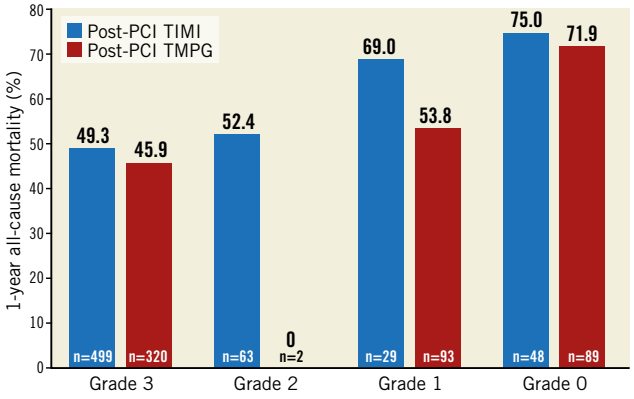


**Figure 3.** *Proportions of one-year all-cause mortality according to post-PCI TIMI flow grade or TMPG.*

**Table 3. Impact on clinical outcomes according to post-PCI TIMI flow grade.**

| Outcome | OR | Lower 95% CI | Upper 95% CI | *p*-value |
|---|---|---|---|---|
| 30-day all-cause mortality | | | | 0.001 |
| TIMI 0 vs TIMI 3 | 2.95 | 1.56 | 5.5 | 0.001 |
| TIMI 1 vs TIMI 3 | 2.55 | 1.16 | 5.6 | 0.019 |
| TIMI 2 vs TIMI 3 | 1.3 | 0.77 | 2.2 | 0.33 |
| 30-day all-cause mortality or renal replacement therapy | | | | 0.002 |
| TIMI 0 vs TIMI 3 | 3.1 | 1.6 | 5.99 | 0.001 |
| TIMI 1 vs TIMI 3 | 2.19 | 0.99 | 4.79 | 0.051 |
| TIMI 2 vs TIMI 3 | 1.19 | 0.7 | 2.01 | 0.52 |
| 1-year mortality | | | | 0.003 |
| TIMI 0 vs TIMI 3 | 3.08 | 1.57 | 6.07 | 0.001 |
| TIMI 1 vs TIMI 3 | 2.29 | 1.02 | 5.12 | 0.044 |
| TIMI 2 vs TIMI 3 | 1.13 | 0.67 | 1.91 | 0.64 |

**Table 4. Impact on clinical outcomes according to post-PCI TMPG.**

| Outcome | OR | Lower 95% CI | Upper 95% CI | *p*-value |
|---|---|---|---|---|
| 30-day all-cause mortality | | | | <0.0001 |
| TMPG 0 vs TMPG 3 | 3.31 | 2.01 | 5.45 | <0.0001 |
| TMPG 1 vs TMPG 3 | 1.64 | 1.03 | 2.61 | 0.037 |
| TMPG 2 vs TMPG 3 | – | – | – | – |
| 30-day all-cause mortality or renal replacement therapy | | | | <0.0001 |
| TMPG 0 vs TMPG 3 | 3.36 | 2.02 | 5.59 | <0.0001 |
| TMPG 1 vs TMPG 3 | 1.54 | 0.97 | 2.46 | 0.066 |
| TMPG 2 vs TMPG 3 | 1.39 | 0.08 | 22.39 | 0.82 |
| 1-year mortality | | | | <0.0001 |
| TMPG 0 vs TMPG 3 | 3.01 | 1.81 | 5.03 | <0.0001 |
| TMPG 1 vs TMPG 3 | 1.37 | 0.86 | 2.17 | 0.184 |
| TMPG 2 vs TMPG 3 | – | – | – | – |

and aOR of 0.46 (95% CI: 0.29-0.72), p<0.001 for TMPG. When included in the same multivariable model, the statistical association of TIMI flow grade with 30-day mortality was offset (aOR 1.27 [95% CI: 0.62-2.64], p=0.51) by the effect of TMPG (aOR 0.38 [95% CI: 0.20-0.71], p=0.002), which remained significant **(Figure 4, Supplementary Table 2)**.

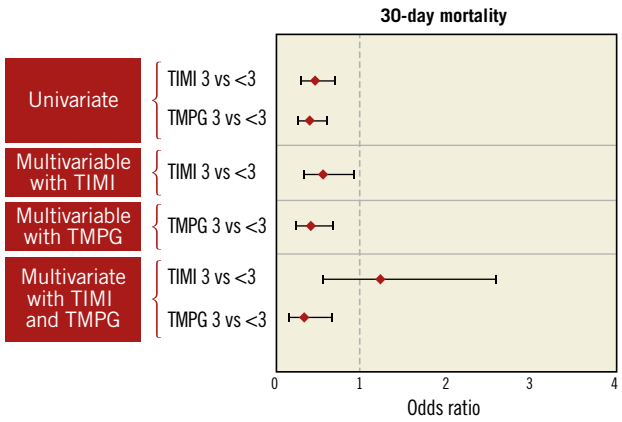


**Figure 4.** *Univariate and multivariable analysis of association of post-PCI TIMI flow grade and TMPG with 30-day all-cause mortality.*

## ANGIOGRAPHIC PARAMETERS AND OTHER ENDPOINTS

Neither TIMI flow grade nor TMPG pre-PCI (3 versus <3 for both parameters) was associated with the composite endpoint of all-cause mortality or RRT at 30 days on univariate analysis (p=0.43 and 0.16, respectively). Both TIMI flow grade and TMPG in the culprit artery after PCI were associated with the composite endpoint of all-cause mortality or RRT at 30 days on univariate analysis. After adjustment for non-angiographic covariates, the association of TMPG remained significant with an aOR of 0.48 (95% CI: 0.30-0.77), p=0.002, while the association of TIMI flow grade did not (aOR 0.73 [95% CI: 0.45-1.18], p=0.20) when included in separate multivariable models. When included in the same multivariable model, TIMI flow grade was not associated with outcome (aOR 1.65 [95% CI: 0.76-3.56], p=0.21) while the association of TMPG remained significant (aOR 0.34 [95% CI: 0.18-0.66], p=0.001) **(Figure 5, Supplementary Table 3)**.

Neither TIMI flow grade nor TMPG pre-PCI (3 versus <3) was associated with one-year mortality on univariate analysis (p=0.98 and 0.27, respectively). Both TIMI flow grade and TMPG in the culprit artery after PCI were associated with one-year all-cause mortality on univariate analysis (p=0.003 and p<0.001, respectively). After adjustment for non-angiographic covariates in separate multivariable models, the association with one-year mortality of both TIMI flow grade and TMPG after PCI was found to be non-significant (p=0.41 for TIMI flow grade and p=0.065 for TMPG). When included in the same multivariable model, TIMI flow grade was not associated with one-year all-cause mortality (p=0.21), while TMPG was significantly associated with the

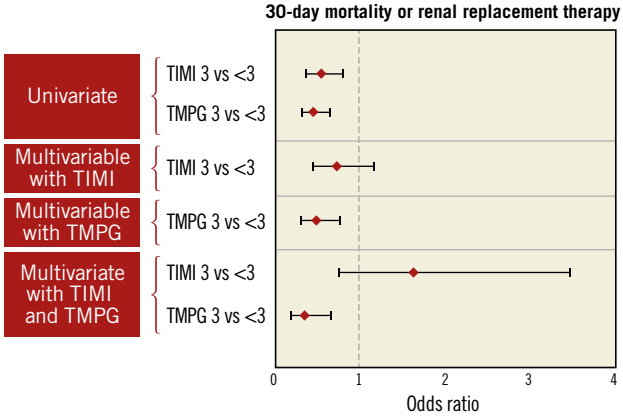


**Figure 5.** *Univariate and multivariable analysis of association of post-PCI TIMI flow grade and/or TMPG (separately then together) with 30-day all-cause-mortality and renal replacement therapy.*

outcome (aOR 0.46 [95% CI: 0.24-0.89], p=0.02) **(Figure 6, Supplementary Table 4)**.

Interestingly, 70 (18.3%) patients with post-PCI TIMI flow grade 3 had TMPG <3, of whom 8 (2.1%) had TMPG 0. Mortality in patients with post-PCI TIMI flow 3 and TMPG 0 was 50% at 30 days and one year. No significant interactions between the PCI strategies (i.e., culprit lesion-only or multivessel PCI) and each angiographic parameter were observed for any outcomes. No difference was noted between characteristics of patients analysed versus those not analysed by the multivariable models which included both TIMI flow grade and TMPG as covariates. No univariate association was found between TIMI flow grade or TMPG and rehospitalisation for heart failure or recurrent MI. The sensitivity analyses were concordant with the main analyses **(Supplementary Table 5)**. No association was found between TIMI flow grade and TMPG (3 versus <3 for both) and RRT (p=0.99 and p=0.12, respectively), recurrent MI (p=0.13 and p=0.99, respectively) or rehospitalisation for heart failure (p=0.13 and p=0.36, respectively) on univariate analysis.

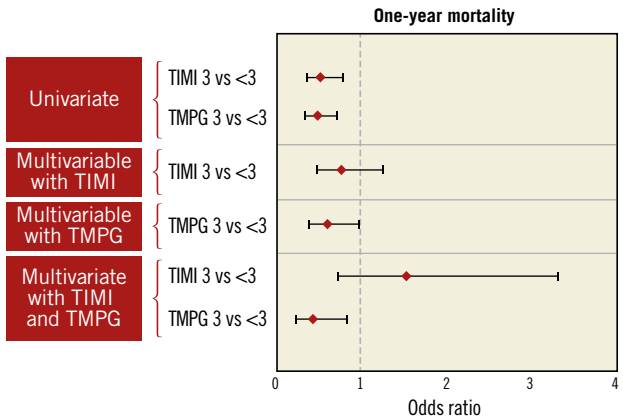


**Figure 6.** *Univariate and multivariable analysis of association of post-PCI TIMI flow grade and/or TMPG (separately then together) with one-year all-cause mortality.*

## Discussion

In this study we report that both TIMI flow grade and TMPG after PCI are associated with all-cause mortality at 30 days in patients presenting with acute MI, multivessel disease and cardiogenic shock. However, when the effect of both angiographic parameters is evaluated jointly in the same model, only TMPG remained associated with mortality at 30 days as well as one year after PCI.

Our results echo those of Mehta et al, who found that post-PCI TIMI flow grade in the culprit artery had a graded inverse relationship with adjusted risk of in-hospital mortality in patients with cardiogenic shock undergoing PCI. Indeed, they found that the OR (95% CI) for TIMI flow grades 0/1 and 2 was 5.47 (95% CI: 4.13 to 7.24) and 2.63 (95% CI: 2.02 to 3.42) compared with TIMI flow grade 3, respectively. However, contrary to Mehta et al, our analysis is more robust because it is based on data extracted from the CULPRIT-SHOCK randomised controlled trial using an angiographic core lab and with rigorous follow-up. Also, the prognostic effect beyond the in-hospital stay and the relationship with TMPG were not previously evaluated by Mehta et al[8].

The strong association of TMPG with the vital status suggests that myocardial microcirculation provides better information than epicardial coronary flow on the efficacy of PCI reperfusion and on the prognosis of these patients admitted in cardiogenic shock. Perhaps unsurprising given previous validation of TMPG as a prognostic marker and infarct size correlate after thrombolysis as well as PCI in MI, our results provide insight for severely ill patients with cardiogenic shock in a contemporary cohort of acute MI patients treated with PCI. The higher prognostic association of TMPG compared to TIMI flow grade after PCI, as attested by our multivariable models, has not been previously described[4-7,14,15]. Approximately one fifth of patients with optimal TIMI flow after PCI in the culprit artery had TMPG <3. Although myocardial microcirculation function can be appreciated angiographically with the TMPG, it can also be estimated through ST-segment elevation resolution in STEMI patients, which has been proposed to have a closer relationship to prognosis than TIMI flow[16]. Operators should consider aiming at optimising the microvascular angiographic result during PCI procedures, and not focus only on the post-procedure TIMI flow grade.

Coronary revascularisation reduces mortality and successful PCI yields better survival in patients with ischaemic cardiogenic shock[3,17]. However, abnormal TIMI flow grade or TMPG at the end of a PCI procedure is associated with worse prognosis. This phenomenon corresponds to slow reflow when partial angiographic filling of vessels is observed, or to no reflow when no flow circulates in the coronary artery. Its mechanism is thought to be associated with atherothrombotic micro-embolisation, reperfusion injury, and spasm. Slow/no reflow has been reported in 10% up to 25% of cases and is associated with high thrombus burden and late reperfusion on admission[18-20]. Intravenous adenosine, calcium channel blockers, and glycoprotein IIb/IIIa inhibitors have been proposed to improve coronary perfusion and reduce infarct size, although the clinical benefit remains unproven[21-25]. Reversing no/slow reflow could reduce myocardial rhythmic susceptibility and size of the myocardial scar, factors associated with early and late mortality. New effective strategies of myocardial protection during the acute phase of MI and of coronary reperfusion are seriously needed.

## Limitations

TIMI frame count (TFC) is another angiographic parameter, along with TIMI flow grade and TMPG, that has been reported to be associated with prognosis after PCI[12]. TFC was unreliable in the CULPRIT-SHOCK core lab database due to insufficient quality of angiographic cines for this parameter. Myocardial blush grade (MBG) is another angiographic surrogate representing coronary microcirculation[26]. Both TMPG and MBG were reported to be correlates of mortality after revascularisation. While MBG can be favoured by clinicians for its simplicity, it was not recorded in the CULPRIT-SHOCK trial. Missing data for angiographic predictors partially impaired the multivariable analyses that included both post-PCI TIMI flow grade and TMPG, with approximately 70% of patients in the analysed population. However, no difference was noted between analysed and non-analysed patients in the multivariable analysis. Angiographic indices were recorded twice (pre and post PCI) by the core laboratory, hence the impact of the different therapeutic interventions (e.g., variations in blood pressure, revascularisation of each vessel) could not be appreciated in a repeated fashion. Developing new strategies to improve microvascular dysfunction after MI is warranted; however, this study does not provide new leads for it.

## Conclusions

The angiographic parameters post-PCI TIMI flow grade and TMPG are associated with mortality after PCI in patients with acute MI and cardiogenic shock. TMPG appears to be a better discriminator than TIMI flow grade to evaluate the success of PCI reperfusion in these cardiogenic shock patients.

## Impact on daily practice

After percutaneous coronary intervention, only TIMI myocardial perfusion grade was independently significantly associated with all-cause mortality at 30 days and one year after adjustment for clinical covariates and TIMI flow grade in this angiographic substudy of the CULPRIT-SHOCK trial. This study provides additional data to support the notion that microcirculation matters more than the epicardial reperfusion after percutaneous coronary intervention in cardiogenic shock patients.

## Appendix. Study collaborators

Benjamin Bertin, MD; Delphine Brugier, MD; Nicolas Vignolles, MD; Georges Hage, MD; Mohamad El Kasty, MD; Mathieu Kerneis, MD; *Sorbonne Université, ACTION Study Group, INSERM UMRS_1166, Institut de cardiologie (AP-HP), Paris, France*. Kurt

Huber, MD; *Wilhelminenspital Kardiologie-Wien, Vienna, Austria*. Marko Noc, MD; *University Medical Centre Ljubljana, Ljubljana, Slovenia*. Marcus Sandri, MD; *Heart Center Leipzig at University of Leipzig and Leipzig Heart Institute, Leipzig, Germany*. Georg Fuernau, MD; *University Heart Center Luebeck, Luebeck, Germany*.

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## Conflict of interest statement

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## Supplementary data

**Supplementary Figure 1.** TIMI myocardial perfusion grades.

**Supplementary Table 1.** Definitions of TIMI myocardial perfusion grades and TIMI flow grades.

**Supplementary Table 2.** Univariate and multivariable analysis of association of post-PCI TFG and TMPG with 30-day all-cause mortality.

**Supplementary Table 3.** Univariate and multivariable analysis of association of post-PCI TFG and TMPG with 30-day all-cause mortality and renal replacement therapy.

**Supplementary Table 4.** Univariate and multivariable analysis of association of post-PCI TFG and TMPG with one-year all-cause mortality.

**Supplementary Table 5.** Multivariable analysis of association of post-PCI TFG and TMPG with the three outcomes. Sensitivity analysis including "as-treated" type of revascularisation as covariable (instead of the randomisation group used for the main multivariable analysis).

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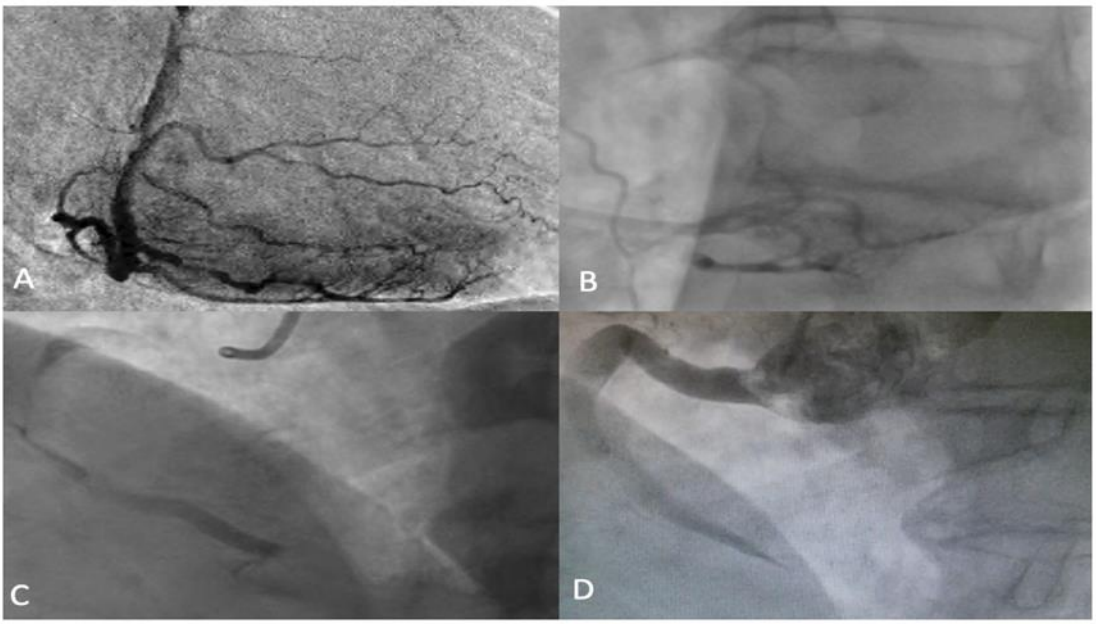
**Supplementary data**




**Supplementary Figure 1.** TIMI myocardial perfusion grades.

A) TMPG grade 3, normal entry and exit of contrast from the microvasculature.

B) TMPG grade 2, delayed entry and exit of contrast from the microvasculature.

C) TMPG grade 1, contrast slowly enters but fails to exit the microvasculature.

D) TMPG grade 0, failure of contrast to enter the microvasculature.

**Supplementary Table 1. Definitions of TIMI myocardial perfusion grades and TIMI flow grades.**

| | |
|---|---|
| **TIMI flow grade** | • TIMI 0 (no perfusion) corresponds to absence of antegrade flow beyond the point of occlusion.<br>• TIMI 1 (penetration without perfusion) corresponds to contrast material passing beyond the area of obstruction but which "hangs up" and fails to opacify the entire coronary bed distal to the obstruction for the duration of the cine angiographic filming sequence.<br>• TIMI 2 (partial perfusion) corresponds to contrast material passing beyond the area of obstruction and opacifying the coronary bed distal to the obstruction, but the rate of entry to or clearance from the distal bed (or both) is perceptibly slower than its entry into or clearance from comparable areas not perfused by the previously occluded vessel (e.g., opposite coronary artery or the coronary bed proximal to the obstruction).<br>• TIMI 3 (complete perfusion) indicates occurrence of antegrade flow into the bed distal to the obstruction as promptly as antegrade flow into the bed proximal to the obstruction, and clearance of contrast material from the involved bed as rapid as clearance from an uninvolved bed in the same vessel or the opposite artery. |
| **TMPG** | • TMPG grade 0 (apparent lack of tissue-level perfusion) corresponds to failure of dye to enter the microvasculature, with either minimal or no ground-glass appearance ("blush") or opacification of the myocardium in the distribution of the culprit artery.<br>• TMPG grade 1 (myocardial blush is present but with no clearance from the microvasculature) corresponds to dye slowly entering but failing to exit the microvasculature, with ground-glass appearance ("blush") or opacification of the myocardium in the distribution of the culprit lesion that fails to clear from the microvasculature, and dye staining present on the next injection (~30 seconds between injections). |

| | |
|---|---|
| | • TMPG grade 2 (myocardial blush clears slowly) indicates delayed entry and exit of dye from the microvasculature, with ground-glass appearance (“blush”) or opacification of the myocardium in the distribution of the culprit lesion that is strongly persistent at the end of the washout phase (i.e., dye is strongly persistent after three cardiac cycles of the washout phase and either does not or only minimally diminishes in intensity during washout).<br>• TMPG grade 3 (myocardial blush clears within three cardiac cycles of washout) indicates normal entry and exit of dye from the microvasculature, with ground-glass appearance (“blush”) or opacification of the myocardium in the distribution of the culprit lesion that clears normally and is either gone or only mildly/moderately persistent at the end of the washout phase (i.e., dye is gone or is mildly/moderately persistent after three cardiac cycles of the washout phase and noticeably diminishes in intensity during the washout phase), similar to that in an uninvolved artery. In that case, blush which is of only mild intensity throughout the washout phase but fades minimally is also classified as grade 3. |

**Supplementary Table 2. Univariate and multivariable analysis of association of post-PCI TFG and TMPG with 30-day all-cause mortality.**

| | OR or aOR | Lower 95% CI | Upper 95% CI | *p*-value |
|---|---|---|---|---|
| **Univariate analysis of angiographic parameters** | | | | |
| TFG 3 (vs <3) | 0.511 | 0.349 | 0.749 | <0.001 |
| TMPG 3 (vs <3) | 0.449 | 0.311 | 0.650 | <0.001 |
| **Multivariable analysis with TFG only** | | | | |
| TFG 3 (vs <3) | 0.608 | 0.380 | 0.971 | 0.037 |
| **Multivariable analysis with TMPG only** | | | | |
| TMPG 3 (vs <3) | 0.457 | 0.290 | 0.719 | <0.001 |
| **Multivariable analysis with TFG and TMPG** | | | | |
| TFG 3 (vs <3) | 1.274 | 0.616 | 2.636 | 0.51 |
| TMPG 3 (vs <3) | 0.378 | 0.202 | 0.708 | 0.002 |

TFG: TIMI flow grade; TIMI: Thrombolysis In Myocardial Infarction; TMPG: TIMI myocardial perfusion grade

**Supplementary Table 3. Univariate and multivariable analysis of association of post-PCI TFG and TMPG with 30-day all-cause-mortality and renal replacement therapy.**

| | OR or aOR | Lower 95% CI | Upper 95% CI | *p*-value |
|---|---|---|---|---|
| **Univariate analysis of angiographic parameters** | | | | |
| TFG 3 (vs <3) | 0.546 | 0.372 | 0.800 | 0.002 |
| TMPG 3 (vs <3) | 0.453 | 0.312 | 0.656 | <0.001 |
| **Multivariable analysis with TFG only** | | | | |
| TFG 3 (vs <3) | 0.725 | 0.446 | 1.180 | 0.20 |
| **Multivariable analysis with TMPG only** | | | | |
| TMPG 3 (vs <3) | 0.477 | 0.298 | 0.766 | 0.002 |
| **Multivariable analysis with TFG and TMPG** | | | | |
| TFG 3 (vs <3) | 1.646 | 0.762 | 3.557 | 0.21 |
| TMPG 3 (vs <3) | 0.338 | 0.175 | 0.655 | 0.001 |

TFG: TIMI flow grade; TIMI: Thrombolysis In Myocardial Infarction; TMPG: TIMI myocardial perfusion grade

**Supplementary Table 4**. **Univariate and multivariable analysis of association of post-PCI TFG and TMPG with one-year all-cause mortality.**

| | OR or aOR | Lower 95% CI | Upper 95% CI | *p*-value |
|---|---|---|---|---|
| **Univariate analysis of angiographic parameters** | | | | |
| TFG 3 (vs <3) | 0.557 | 0.379 | 0.820 | 0.003 |
| TMPG 3 (vs <3) | 0.522 | 0.360 | 0.755 | <0.001 |
| **Multivariable analysis with TFG only** | | | | |
| TFG 3 (vs <3) | 0.817 | 0.504 | 1.324 | 0.41 |
| **Multivariable analysis with TMPG only** | | | | |
| TMPG 3 (vs <3) | 0.642 | 0.401 | 1.027 | 0.065 |
| **Multivariable analysis with TFG and TMPG** | | | | |
| TFG 3 (vs <3) | 1.631 | 0.759 | 3.505 | 0.21 |
| TMPG 3 (vs <3) | 0.462 | 0.242 | 0.885 | 0.019 |

TFG: TIMI flow grade; TIMI: Thrombolysis In Myocardial Infarction; TMPG: TIMI myocardial perfusion grade

**Supplementary Table 5. Multivariable analysis of association of post-PCI TFG and TMPG with the three outcomes. Sensitivity analysis including "as-treated" type of revascularisation as covariable (instead of the randomisation group used for the main multivariable analysis).**

| | 30-day mortality | | | 30-day mortality or RRT | | | One-year mortality | | |
|---|---|---|---|---|---|---|---|---|---|
| | **aOR** | **95% CI** | ***p*-value** | **aOR** | **95% CI** | ***p*-value** | **aOR** | **95% CI** | ***p*-value** |
| **Multivariable analysis with TFG only** | | | | | | | | | |
| TFG 3 (vs <3) | 0.594 | 0.372-0.949 | 0.029 | 0.704 | 0.433-1.147 | 0.16 | 0.800 | 0.493-1.299 | 0.37 |
| **Multivariable analysis with TMPG only** | | | | | | | | | |
| TMPG 3 (vs <3) | 0.453 | 0.287-0.713 | <0.001 | 0.468 | 0.291-0.754 | 0.002 | 0.635 | 0.396-1.018 | 0.059 |
| **Multivariable analysis with TFG and TMPG** | | | | | | | | | |
| TFG 3 (vs <3) | 1.199 | 0.578-2.488 | 0.63 | 1.531 | 0.706-3.321 | 0.28 | 1.555 | 0.723-3.348 | 0.26 |
| TMPG 3 (vs <3) | 0.388 | 0.207-0.729 | 0.003 | 0.346 | 0.177-0.674 | 0.002 | 0.470 | 0.244-0.902 | 0.023 |

RRT: renal replacement therapy; TFG: TIMI flow grade; TIMI: Thrombolysis In Myocardial Infarction; TMPG: TIMI myocardial perfusion grade