Journal of Inflammation

RESEARCH

Open Access

Prehospital pulse-dose glucocorticoid on index of microvascular resistance in patients with ST-segment elevation myocardial infarction: a sub-study of the PULSE-MI trial

Jasmine Melissa Marquard[1*], Jacob Lønborg[1,2], Laust Emil Roelsgaard Obling[1], Rasmus Paulin Beske[1], Yan Zhou[1], Lars Nepper-Christensen[1], Niels Vejlstrup[1], Lia Evi Bang[1], Christian Hassager[1,2], Fredrik Folke[2,3,4], Lars Bredevang Andersen[5], Helle Collatz Christensen[2,5], Lene Holmvang[1,2], Frants Pedersen[1], Ole Ahlehoff[1], Reza Jabbari[1], Mikko Minkkinen[1], Rikke Sørensen[1,2], Hans-Henrik Tilsted[1] and Thomas Engstrøm[1,2]

Abstract

Background Microvascular injury in patients with ST-segment elevation myocardial infarction (STEMI) occurs in up to 50%, yet no therapeutic target exists. Inflammation contributes directly to myocardial damage in STEMI and may also cause deleteriously effects on the microcirculation. The aim of this prespecified sub-study was to determine the effect of prehospital pulse-dose glucocorticoid on the microcirculation determined by index of microvascular resistance (IMR) and its relation to inflammation.

The PULSE-MI trial was a 1:1 randomized, blinded, placebo-controlled clinical trial in patients with STEMI transferred for primary percutaneous coronary intervention (PCI) investigating the cardioprotective effects of prehospital pulse-dose glucocorticoid (methylprednisolone 250 mg) compared with placebo. In this prespecified sub-study, we investigated microvascular function as IMR by thermodilution after primary PCI and inflammation defined by C-reactive protein (CRP) at 24 hours after onset of STEMI.

Results Of 530 patients included in the PULSE-MI trial, 295 (56%) were assessed with coronary physiology of whom 142 (48%) were treated with glucocorticoid and 153 (52%) with placebo. Baseline characteristics were overall well-balanced in both groups. The median IMR in the glucocorticoid group was 23 (interquartile range (IQR), 11-38) and 18 (IQR, 11-42) in the placebo group (p=0.49). CRP upon arrival did not differ between treatment groups (p=0.81), but CRP at 24 hours was significantly lower in the glucocorticoid group compared to placebo (p<0.001).

Conclusions Prehospital glucocorticoid did not impact IMR assessed immediately after primary PCI, albeit this compound, demonstrated significant anti-inflammatory effects as determined by CRP levels at 24 hours.

*Correspondence:
Jasmine Melissa Marquard
jasmine.melissa.marquard@regionh.dk
Full list of author information is available at the end of the article

Trial registration http://www.clinicaltrials.gov; Unique Identifier: NCT05462730.
Keywords STEMI, Inflammation, Microvascular damage, Randomized clinical trial

Introduction

Restoration of epicardial blood flow with primary percutaneous coronary intervention (PCI) is pivotal to salvage myocardium at risk in ST-segment elevation myocardial infarction (STEMI) [1]. In patients with STEMI, reperfusion of the epicardial artery may not necessarily signify successful treatment, as microvascular damage occurs in up to half of patients with STEMI resulting in microvascular dysfunction [2].

Myocardial and microvascular damage including intramyocardial hemorrhage assessed by cardiac magnetic resonance (CMR) has shown to predict long-term outcomes following STEMI [3]. Function of the microcirculation can also be assessed directly by thermodilution-derived intracoronary physiology measuring coronary flow reserve (CFR) and the index of microvascular resistance (IMR) which is an index of minimal microvascular resistance [4, 5]. Thus, IMR represents an index corresponding to flow and microvascular damage [5]. IMR measured immediately after primary PCI has shown to be a strong indicator of microvascular dysfunction and is a prognostic predictor for major cardiovascular events after STEMI [4]. Despite novel non-invasive and invasive modalities of assessing microvascular damage, prevention and treatment hereof remains a perpetual challenge.

The cause of microvascular damage in STEMI is multifactorial but potentially includes distal embolization, vasospasm, and lethal reperfusion injury [6]. Inflammation is initiated immediately after acute ischemia and further exacerbated following reperfusion, and inflammation has been linked to extensive microvascular damage [7, 8]. High-dose glucocorticoids exert broad anti-inflammatory effects with several immunomodulatory activities that is of positive influence in acute diseases [9–11]. In addition to the anti-inflammatory effects, glucocorticoids may exhibit stabilizing, acute effects at high doses (> 100 mg), known as the *non-genomic* effect [12]. These actions are proposed to confer cardioprotection by cell membrane stabilization and reducing infarct size [12]. Whether the anti-inflammatory properties along with the non-genomic effects of pulse-dose glucocorticoids in the prehospital setting, prior to reperfusion, translate into less microvascular dysfunction remains unknown.

In patients with STEMI, we conducted a randomized, blinded, placebo-controlled clinical trial "Prehospital Pulse Glucocorticoid Therapy in Patients with ST-Segment Elevation Myocardial Infarction" (PULSE-MI) to investigate the cardioprotective effects of glucocorticoids evaluated by CMR [13]. The trial found no effect of glucocorticoid on final infarct size at three months, but glucocorticoids reduced acute infarct size and improved acute left ventricular ejection fraction. In addition, less presence of microvascular obstruction was observed in these patients [14]. The present prespecified sub-study of the PULSE-MI trial aimed to investigate the effect of prehospital pulse-dose glucocorticoid in patients with STEMI on the microcirculation.

Methods

Trial design

This was a prespecified sub-study of the PULSE-MI trial (Prehospital Pulse Glucocorticoid Therapy in Patients with ST-Segment Elevation Myocardial Infarction). The trial was a blinded, placebo-controlled, randomized clinical trial investigating the cardioprotective effect of prehospital pulse-dose glucocorticoid in patients with STEMI transferred for primary PCI [13]. The trial was conducted at the Department of Cardiology, Rigshospitalet, Denmark and all patients were randomized in the prehospital setting by the Emergency Medical Services in Region Zealand and Capital Region of Denmark. The trial was registered at https://clinicaltrials.gov (Unique Identifer: NCT05462730) and approved in the Clinical Trials Information System (EU-CT number: 2022–500762-10–00) and by the Danish Data Protection Agency (ID: P-2022–280). The trial protocol and primary results have previously been published [13, 14]. The trial was conducted in compliance with the Helsinki Declaration, European and national laws. The conduct of the trial was monitored by the Good Clinical Practice unit of Copenhagen, Denmark and monitored for safety and efficacy by an independent Data and Safety Monitoring Board. All patients provided informed consent following the acute treatment according to European law [13].

Patients

Between November 2022 and October 2023, patients with STEMI [1], aged ≥ 18 years and < 12 h of symptoms were randomized and treated in the ambulance prior to acute coronary angiogram. Main exclusion criteria were out-of-hospital cardiac arrest, previous acute myocardial infarction in assumed culprit, and a history of maniac/psychotic episodes. The full list eligibility criteria and study design have been published [13]. Of 742 randomized patients, 530 patients with STEMI were included in the modified intention-to-treat population [14].

Intervention and randomization

Patients were randomized in the prehospital setting to a single injection of methylprednisolone 250 mg (2 × 125 mg/2 mL) (glucocorticoid group) or placebo (0.9% NaCl 4 mL). The study medicine (active or placebo) was administered as a bolus injection over a period of 5 min as soon as the patient was accepted for an acute coronary angiogram at Rigshospitalet. Randomization was done using a random number generator with allocation in a 1:1 ratio. All ambulances throughout Region Zealand and Capital Region of Denmark were equipped with identical, opaque study medicine boxes, each numbered randomly according to allocation. Prehospital study medicine was administered by the ambulance staff who was blinded when randomly picking a study medicine box. The treating ambulance staff was unblinded after opening the box. All in-hospital personnel, trial investigators, and the patients were blinded for treatment allocation. All patients included in the trial were otherwise treated according to guidelines and standard procedures [1].

Outcome measures and objectives

This prespecified sub-study encompassed patients with invasive coronary physiology assessment following primary PCI. The objective was to determine the effect of prehospital pulse-dose glucocorticoid compared with placebo on the microcirculation determined by IMR in the culprit artery following primary PCI. Moreover, we sought to investigate the relation between microvascular function and randomized treatment using CMR, intracoronary physiology, and inflammation using C-reactive protein (CRP) levels.

Coronary physiology

Coronary physiology was assessed in eligible patients at the discretion of the operator and was assessed immediately following primary PCI. Coronary physiology was performed during all hours and during weekends. The theoretical basis of the physiological thermodilution-derived indices have been published elsewhere [15]. In brief, thermodilution-derived indices were measured by a pressure/temperature gauge guidewire (PressureWire X; Abbott) and data from the guidewire were analyzed with dedicated software (CoroFlow v.3.01; Coroventis). Equalization of the wire pressure and aortic pressure was done with the pressure sensor positioned at the tip of the guide catheter after it was secured that damping was not present. The wire was subsequently advanced to the distal third of the vessel. The mean transit time (Tmn) was calculated from the thermodilution curves by bolus injections of room temperature saline (3 mL) at rest and during maximal hyperemia. The Tmn was measured three times at rest and during maximal hyperemia, and the average Tmn was calculated by the computer in each physiological state. The software automatically marked any recordings of Tmn, deviating with more than 30% from the average value. If a recording was marked, the measurement for the specific recording was repeated. A two-minute infusion of adenosine (140 µg/kg/min) in a large vein was used to induce maximal hyperemia. IMR, reflecting the minimal microcirculatory resistance, was defined as the mean distal pressure multiplied by Tmn during maximal hyperemia [5].

Blood samples and cardiac magnetic resonance

CRP was collected upon admission by arterial blood samples. Between 12 and 36 h of symptom debut, CRP was collected using venous blood samples and the sample closest to 24 h was used for all analyses in this sub-study.

The CMR protocol and analyses has been described [13]. In brief, patients underwent two CMR scans, one during admission and three months after STEMI. This sub-study only included CMR outcomes of the acute scan, as glucocorticoid improved acute CMR outcomes in the primary analysis. Infarct size was measured by late gadolinium enhancement on short axis images performed 6–10 min following contrast infusion using a 5 standard deviations (SD) threshold of visually identified remote healthy myocardium on each short axis slice [16]. Microvascular obstruction was defined as hypointense areas within the infarct region [17]. $T2^*$-images prior to contrast injection were used to identify intramyocardial hemorrhage defined as either hypointense regions within the infarcted area with mean $T2^*$-value > 2 SD below $T2^*$-value of remote healthy myocardium [18], or $T2^*$-value within the infarcted area of ≤ 20 [19]. All quantitative analyses were performed in circle cardiovascular imaging (CVI42) by a reader blinded to clinical data.

Statistical analysis

Continuous variables were presented as mean (SD) if parametric and median (interquartile range (IQR)) if non-parametric. Categorical variables were presented as numbers and percentages. To investigate differences between groups, the Wilcoxon Rank sum test was used for numeric variables and Chi-square or Fishers test for categorical variables, as appropriate.

Box plots showing distributions of CRP at 24 h and IMR in the glucocorticoid and placebo group were conducted. Linear regression was used to investigate the relation between both IMR and CRP at 24 h, and treatment allocation. Logarithmic transformation was used to improve normality. Interaction analysis with culprit artery was performed to elucidate the potential difference of IMR in the treatment arms according to culprit artery. Interaction analysis between IMR and CRP at 24 h according to treatment arm was performed to elucidate

the relation between microvascular damage and inflammation. To investigate the microvascular function and inflammation in relation to CMR outcomes according to treatment arm, interaction analyses between IMR, CRP, and CMR outcomes (acute and final infarct size, microvascular obstruction, intramyocardial hemorrhage, left ventricular ejection fraction) were performed. In all interaction analyses, linear regression was used for numeric outcomes, whereas logarithmic regression was used for binary outcomes.

As judged by the operator, not all patients had coronary physiology assessed. To investigate potential differences between these patients and those with coronary physiology, a baseline table stratified by coronary physiology assessment was conducted.

IMR and CMR outcomes were assessed in patients with and without pre-infarction angina in the treatment groups. Pre-infarction angina was defined as episodes of chest pain < 48 before symptom onset.

The *P*-values were two-sided and considered statistically significant if less than 0.050. All statistical analyses were performed in R Studio, version 4.3.2 (RStudio Team [2020]. RStudio: Integrated Development for R. RStudio, PBC, Boston, MA; URL: http://www.rstudio.com/).

Results

Of 530 patients included in the modified intention-to-treat population of the PULSE-MI trial, a total of 295 (56%) had invasive physiology following primary PCI of whom 142 patients were treated with glucocorticoid and 153 with placebo (Fig. 1). Baseline characteristics stratified by assessment of coronary physiology are presented in Supplementary Table 1. Patients without coronary physiology were older, had higher heart rate in the prehospital setting, higher Killip Class at admission, and more often culprit in left main or left anterior descending artery (LAD).

In patients assessed for coronary physiology, baseline characteristics were overall well-balanced in the treatment groups besides lactate on arrival (glucocorticoid: 1.80 (IQR, 1.50 to 2.40) vs. placebo: 1.60 (IQR, 1.20 to 2.30), $p = 0.010$) (Table 1). The median age was 62 years (IQR, 55 to 71) and 82% were men, the culprit lesion was LAD in 42%, 56% had thrombolysis in myocardial infarction flow 0–1 before PCI, and the overall duration from symptom to study intervention was 105 min (IQR, 66 to 222).

Distribution of IMR values in both treatment groups is presented in Fig. 2. There was no difference in IMR between the glucocorticoid (23 (IQR, 11 to 38)) and placebo (18 (IQR, 11 to 42)) group ($p = 0.49$) (Table 2). Differences in IMR between treatment groups in linear regression remained non-significant ($p = 0.74$) and there was no interaction with culprit lesion ($p = 0.71$). Associations between IMR and CMR outcomes were similar in both treatment groups (Fig. 3). There was no interaction between IMR and glucocorticoid treatment regarding acute infarct size ($p = 0.82$), microvascular obstruction

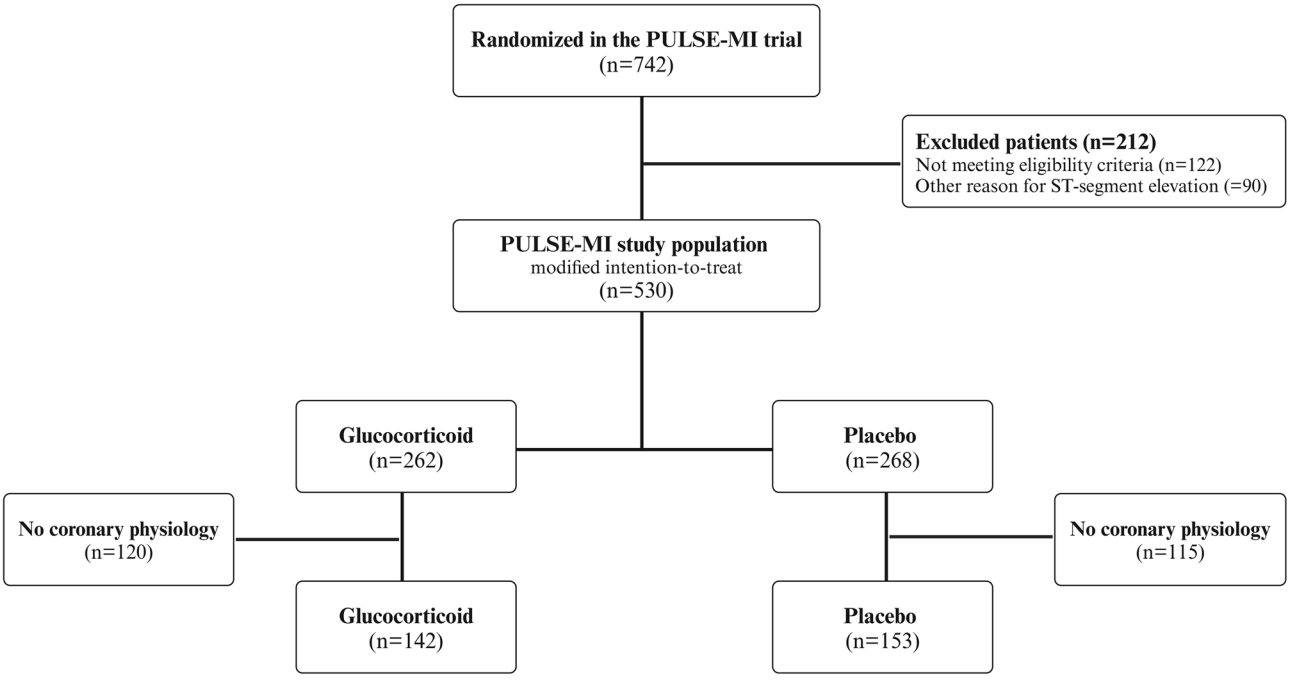

Fig. 1 Flowchart of the study population. Legend: The modified intention-to-treat population included all patients who fulfilled all eligibility criteria. Excluded patients include all post-randomization exclusions with comprises patients who were randomized but either did not fulfill eligibility criteria or had other reasons for ST-segment elevation

Table 1 Baseline characteristics

Variable	Randomization		*p*-value*
	Glucocorticoid (*n* = 142)	Placebo (*n* = 153)	
Demographics			
Age, years, median (IQR)	62 (54, 72)	62 (55, 71)	0.94
Male sex, n (%)	113 (80)	130 (85)	0.23
BMI, kg/m2, median (IQR)	27.1 (24.3, 29.4)	26.7 (24.5, 29.9)	0.83
Comorbidities, n (%)			
Smoking			
Current	55 (39)	65 (42)	0.51
Previous	48 (34)	40 (26)	0.15
Never	40 (27)	48 (31)	0.46
Predisposition to ischemic heart disease	54 (38)	58 (38)	0.98
Hypertension	51 (36)	64 (42)	0.30
Peripheral arterial disease	1 (0.7)	3 (2.0)	0.62
Hypercholesterolemia	35 (25)	51 (33)	0.10
Previous stroke or transient ischemic attack	2 (1)	7 (5)	0.18
Diabetes mellitus	15 (11)	22 (14)	0.32
Previous myocardial infarction	5 (4)	6 (4)	0.86
Prehospital			
Anterior infarction, n (%)	58 (41)	62 (41)	0.54
Cardiac arrest with shockable rhythm, n (%)	6 (4)	3 (2)	0.32
Nitroglycerine, n (%)	124 (87)	136 (89)	0.68
Acetylsalicylic acid, n (%)	142 (100)	152 (99)	1.00
Heparin, n (%)	142 (100)	151 (99)	0.50
Arrival			
Pre-infarction angina, n (%)	42 (30)	57 (37)	0.16
Killip class > I, n (%)	4 (3)	8 (5)	0.30
Left ventricular ejection fraction, %, median (IQR)	45 (35, 55)	45 (35, 55)	1.00
Heart rate, bpm, median (IQR)	74 (66, 85)	75 (64, 87)	0.77
Systolic blood pressure, mmHg, median (IQR)	133 (114, 150)	140 (120, 155)	0.07
Diastolic blood pressure, mmHg, median (IQR)	75 (65, 82)	75 (67, 85)	0.38
Lactate, mmol/L, median (IQR)	1.80 (1.50, 2.40)	1.60 (1.20, 2.30)	0.018
Glucose, mmol/L, median (IQR)	8.30 (7.20, 9.55)	8.00 (7.00, 9.60)	0.18
Time durations, median (IQR)			
Symptom to study intervention, mins	113 (75, 202)	104 (62, 235)	0.81
Symptom to first wire, mins	188 (132, 280)	171 (123, 305)	0.56
Study intervention to first wire, mins	62 (80, 117)	58 (80, 115)	0.43
Procedural data			
Admission during off-hour**	82 (58%)	92 (60%)	0.77
Radial access, n (%)	140 (99)	150 (98%)	1.00
Culprit lesion, n (%)			0.57
Left anterior descending artery	58 (41)	66 (43)	
Circumflex artery	27 (19)	22 (14)	
Right coronary artery	57 (40)	65 (42)	
Pre-PCI TIMI flow 0-I, n (%)	83 (58)	82 (54)	0.40
Post-PCI TIMI flow III, n (%)	138 (97)	149 (97)	1.00
Lesion Type, n (%)			0.53
Type A	1 (1)	3 (2)	
Type B1	15 (11)	13 (9)	
Type B2	77 (54)	92 (60)	
Type C	49 (35)	45 (29)	
Multivessel disease, n (%)	80 (56)	81 (53)	0.56
Use of glycoprotein IIb/IIIa inhibitor, n (%)	12 (9)	7 (5)	0.18

Table 1 (continued)

Variable	Randomization		*p*-value*
	Glucocorticoid (*n* = 142)	Placebo (*n* = 153)	
Primary treatment with DES, n (%)	142 (100)	147 (96)	0.06
Total stent length in the culprit lesion, median (IQR)	33 (25, 48)	32 (23, 43)	0.12
Largest balloon diameter, median (IQR)	4.25 (4.00, 4.50)	4.00 (4.00, 4.50)	0.41
Thrombus aspiration, n (%)	0 (0)	4 (3)	0.12
Use of intracoronary imaging, n (%)	73 (51)	76 (50)	0.81

Percentages may not total 100 because of rounding

BMI body mass index, *DES* drug-eluting stent, *IQR* interquartile range, *PCI* percutaneous coronary intervention, *TIMI* thrombolysis in myocardial infarction

*Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

**Off-hour was defined as procedure start outside the time window of 08:00am to 03:00pm

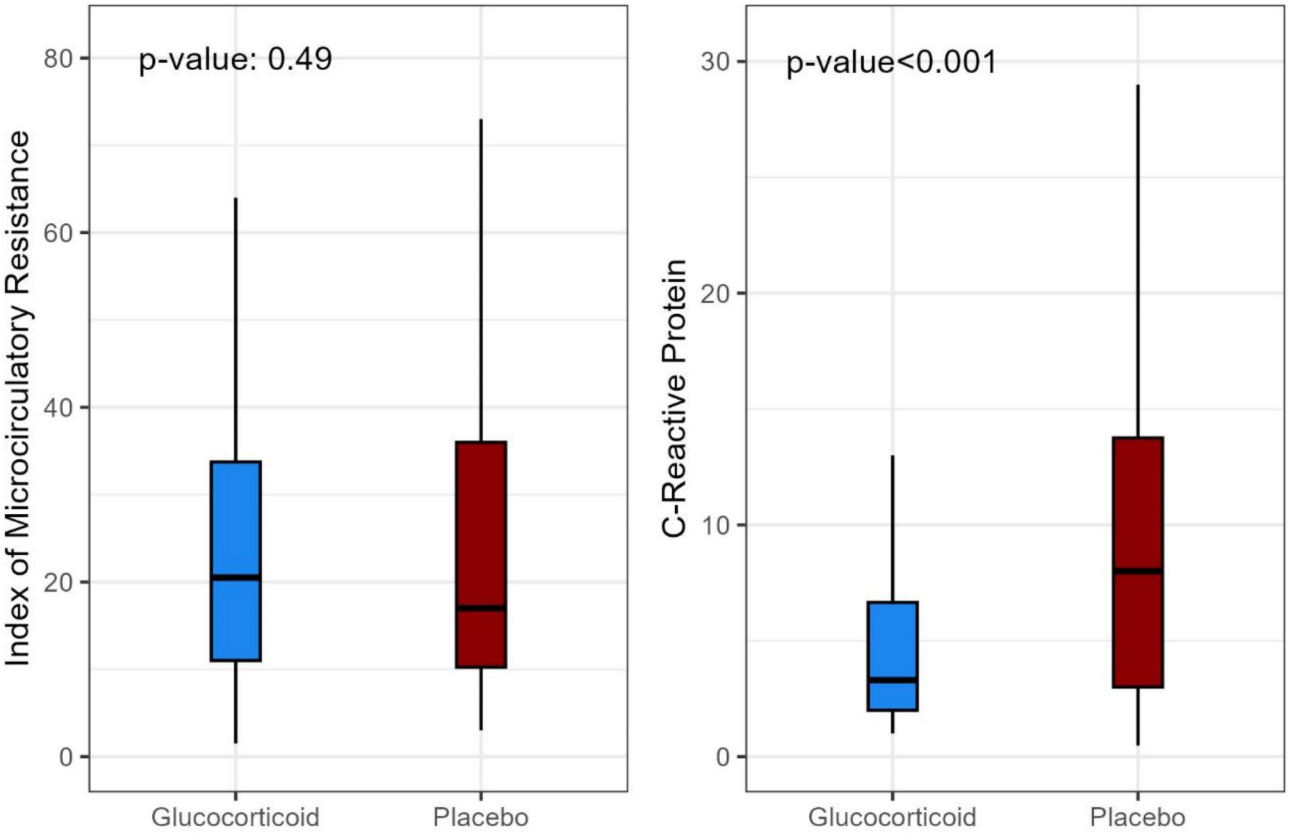

Fig. 2 Distribution of index of microvascular resistance and C-reactive protein. Legend: Shown are two box plots of the distribution of C-reactive protein (CRP) and index of microvascular resistance (IMR). Boxplots show median, lower and upper quartile for each group. The line within the box is the median and the upper and lower edge of the box is the upper and lower quartile, respectively. The blue presents the glucocorticoid group whereas the red presents the placebo group. CRP was measured in mg/L at 24 hours

Table 2 Microvascular assessment

	n	Randomization			*p*-value*
		Glucocorticoid	n	Placebo	
Coronary Physiology, median (IQR)					
Fractional Flow Reserve	142	0.97 (0.94, 0.99)	153	0.96 (0.92, 0.99)	0.24
Coronary Flow Reserve	142	1.60 (1.10, 2.30)	153	1.70 (1.30, 2.30)	0.15
Index of Microvascular Resistance	142	23 (11, 38)	153	18 (11, 42)	0.49

IQR interquartile range

*Wilcowon Rank sum test

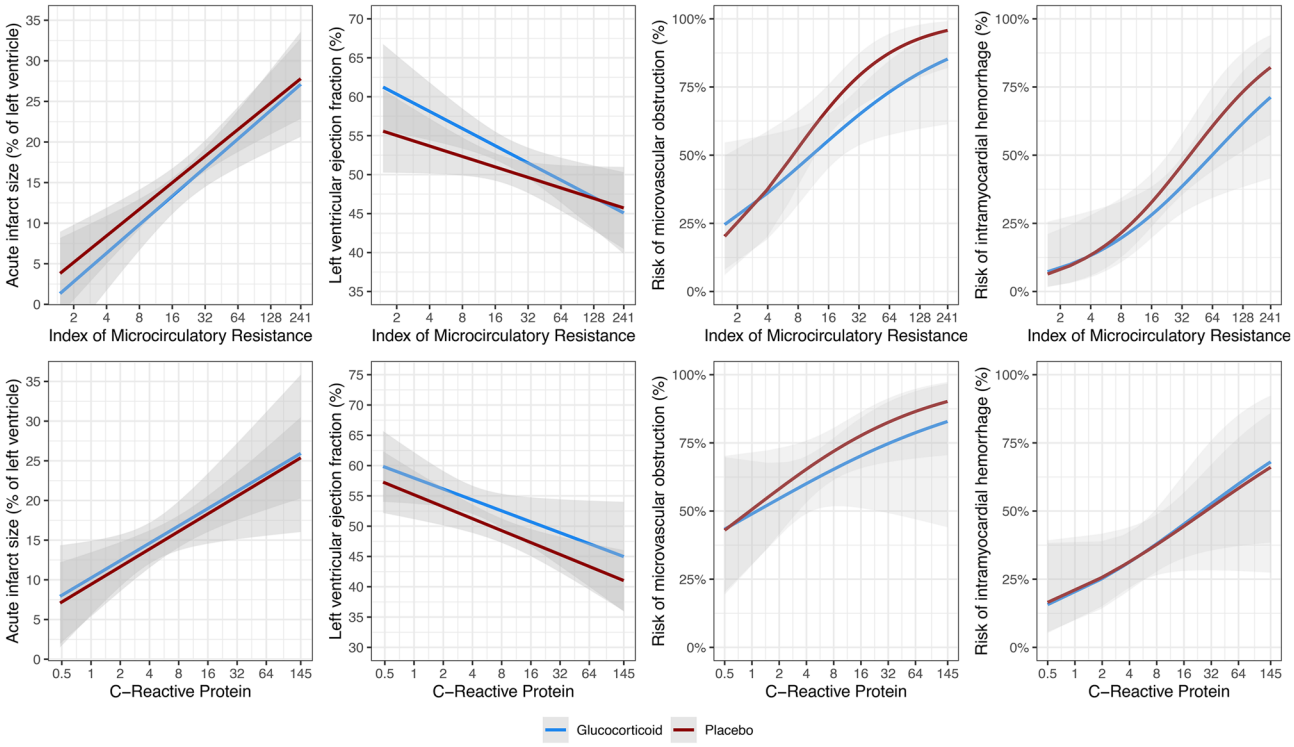

Fig. 3 Associations between microvascular function, inflammation, and cardiac magnetic resonance outcomes. Legend: The upper row shows index of microvascular resistance on x-axis and associations to acute cardiac magnetic resonance outcomes on y-axis. The lower row shows C-reactive protein (CRP) on x-axis and associations to acute cardiac magnetic resonance outcomes on y-axis. Blue lines are the glucocorticoid group and red line is the placebo group. All x-axes are transformed using logarithmic transformation. CRP was measured in mg/L at 24 hours

($p = 0.40$), intramyocardial hemorrhage ($p = 0.68$), or left ventricular ejection fraction ($p = 0.08$) between treatment groups. Figure 3 shows the association between IMR and CMR outcomes. In both treatment groups, elevated IMR was associated with larger infarct size, more presence of microvascular obstruction and intramyocardial hemorrhage, and lower left ventricular ejection fraction.

In analysis stratified by pre-infarction angina, there was no difference between IMR values in the two treatment groups (Supplementary Table 2). Patients with pre-infarction angina and were treated with glucocorticoids had less microvascular obstruction, smaller infarct size and higher left ventricular ejection fraction compared to patients treated with placebo (Supplementary Table 2).

CRP at arrival did not differ between treatment groups (glucocorticoid: 3 (IQR, 1 to 4), placebo: 2 (IQR, 1 to 5), $p = 0.81$). CRP at 24 h was significantly lower in the glucocorticoid group (4 (IQR, 2 to 10)) compared with the placebo group (11 (IQR, 4 to 21)) $p < 0.001$. There was no interaction between CRP at 24 h and IMR according to treatment group ($p = 0.58$). In both treatment groups, an increased CRP was associated with larger acute infarct size and lower left ventricular ejection fraction (Fig. 3), and no interaction was found in either analysis ($p = 0.97$) and ($p = 0.87$), respectively. There was no interaction between CRP at 24 h and presence of microvascular obstruction ($p = 0.72$) or intramyocardial hemorrhage ($p = 0.93$) according to treatment group.

Discussion

This was a prespecified sub-study of the PULSE-MI trial, evaluating the acute effects of prehospital glucocorticoid on the microcirculation in patients with STEMI. Compared to placebo, prehospital pulse-dose glucocorticoid did not affect IMR but had significant anti-inflammatory effects determined by a significant CRP reduction.

Elevated microvascular resistance evaluated by IMR and presence of microvascular obstruction on CMR show concordance in the majority of patients with STEMI [4]. IMR serves as a functional measure of the hyperemic resistance in the microcirculation and can be used to directly identify microvascular dysfunction in the artery subtending myocardium at risk [4]. When assessed acutely, IMR reflects functional impairment of both reversible damage such as edema or stunning of the myocardium, as well as irreversible damage caused by cellular necrosis [20]. Conversely, microvascular obstruction on CMR is an anatomic impairment representing a severe perfusion defect and thus represent an irreversible damage [17]. Intuitively, glucocorticoid could prevent both but in this sub-study, no effect of prehospital glucocorticoid on IMR was found. However, as reported

in the main trial, prehospital glucocorticoid on the other hand was associated with less microvascular obstruction [14]. Previous studies found varying discordance between IMR and microvascular obstruction [4]. One reasonable explanation is that IMR measured immediately after the acute phase of STEMI with primary PCI change rapidly over time and thus may not be representative at the time when CMR is performed [4]. In this study, IMR was assessed immediately after primary PCI while microvascular obstruction was assessed on CMR conducted in the following 6–24 h after STEMI. The discordance between the two measures, IMR and microvascular obstruction, may therefore simply be explained by the different time of assessment.

In the acute phase of STEMI, inflammation is a potential deleterious component contributing to excessive microvascular damage [7]. The inflammatory damage is especially significant in relation to reperfusion, affecting the endothelial and myocardial cells and thus their integrity [2]. This study investigated the broad acting anti-inflammatory drug, glucocorticoid, given as pulse-dose in the prehospital setting to alleviate the rapid acting non-genomic effects of glucocorticoid, prior to reperfusion [13]. Our findings showed that 24 h CRP levels were significantly lower after treatment with glucocorticoid, and thus glucocorticoid, with high probability, had an anti-inflammatory effect. In addition, CRP levels associated with microvascular obstruction supporting the relationship between the inflammatory level and microvascular damage [2]. However, no effect of prehospital glucocorticoid on CRP measured upon arrival was observed. Our findings support more prolonged effect of the compound which become evident when microvascular obstruction is measure using CMR. Still in this context, our data on IMR suggest that glucocorticoid do not exert rapid effects to mitigate microvascular damage. This view is challenged, however, since lactate upon arrival was significantly higher in the glucocorticoid group compared to placebo. Increased lactate is a natural physiological response to glucocorticoid administration due to its effect on the glucose metabolism [21]. This emphasize that glucocorticoid initiated rapid cellular processes very early after administration. Of note, lactate accumulates during ischemia, leading to decreased myocardial intracellular pH levels [6]. During reperfusion, lactate is washed out and physiological pH is rapidly restored, a process referred to as *lethal reperfusion injury* as the dramatic change in intracellular pH causes additional cardiomyocyte death [6]. Therefore, the higher lactate levels in the glucocorticoid group support the existence of an acidic environment for a prolonged period of time during reperfusion and may play a cardioprotective role. Of note, the main trial showed smaller acute infarct size, higher left ventricular ejection fraction and less microvascular obstruction compared to placebo [14]. The above suggestions together with the fact that IMR was unaffected by glucocorticoid could indicate that the acute beneficial effects of prehospital glucocorticoid in STEMI manifest at a direct myocardial cellular level with no effect on microvascular hyperemic flow and IMR. Remarkably, these findings are in line with experimental studies of pulse-dose glucocorticoid cellular effects in the myocardium and they may explain the discrepancy between functional microvascular dysfunction determined by IMR and anatomical microvascular damage as defined by acute CMR [12, 22].

Several studies have investigated pharmacological therapies aimed at preventing microvascular damage in STEMI [23]. Yet, no larger, blinded, randomized trial exists on pharmacological therapies aimed at improving IMR following primary PCI. In a non-blinded, randomized trial in forty-one patients with STEMI, streptokinase administered prior to primary PCI reduced IMR two days following PCI but failed to show improvement in left ventricular function [24]. In another open-label, randomized trial including 110 patients with STEMI, ticagrelor was non-superior to prasugrel in improving IMR at baseline and after one month, infarct size, and microvascular obstruction but showed less intramyocardial hemorrhage in the ticagrelor group [25]. Thus, the majority of trials have focused on an antithrombotic or fibrinolytic strategy to reduce microvascular damage and have shown varying results. In this study, IMR may therefore reflect the acute microcirculatory state whereas previous studies could reflect the potential recovery on the microvascular function [26]. Taken altogether, any future study with IMR as an endpoint should cautiously consider the optimal timing of IMR measurement.

Finally, this sub-study suggest that acute anti-inflammatory treatment prevents microvascular obstruction on CMR independent of IMR assessed directly following primary PCI [14]. However, the role of anti-inflammatory treatment in prevention and treatment of microvascular damage warrants future randomized trials to delineate its efficacy in the setting of STEMI.

Study limitations

There are some limitations to this sub-study. The blood used for analysis was peripheral blood which may not reflect the inflammatory processes in the infarcted myocardium directly. Moreover, there may be a risk of selection bias as not all patients in each randomization group had invasive physiology assessed at the discretion of the operator due to either slow/no reflow, logistics, or low blood pressure. Patients with no coronary physiology assessment were sicker than patients who had coronary physiology assessment. The IMR findings of this sub-study may therefore be confounded by selection bias.

In addition, microvascular obstruction was assessed on acute CMR which was performed within a median of one day after STEMI. Thus, we cannot rule out that microvascular obstruction develops further beyond this point. However, the presence of microvascular obstruction in this study is similar to previous studies [17]. The IMR values in this study were lower than in other studies [4, 27]. This suggests that the patients included in this study may represent a lower risk population. Finally, IMR may be limited by its operator dependency with a high variability and may not be as precise as measurement of absolute microvascular resistance which may be more reliable [26].

Conclusions

Prehospital glucocorticoid did not impact IMR assessed immediately after primary PCI, albeit this compound, demonstrated significant anti-inflammatory effects as determined by CRP levels at 24 h.

Abbreviations

CFR	Coronary Flow Reserve
CMR	Cardiac magnetic resonance
CRP	C-reactive protein
IMR	Index of Microvascular Resistance
LAD	Left anterior descending coronary artery
PCI	percutaneous coronary intervention
PULSE-MI	Prehospital Pulse Glucocorticoid Therapy in Patients with ST-Segment Elevation Myocardial Infarction
STEMI	ST-segment elevation myocardial infarction
TIMI	Thrombolysis in myocardial infarction
Tmn	Mean transit time

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12950-025-00440-2.

Supplementary Material 1.

Acknowledgements

We would like to thank all personnel at the ambulance staff in the Emergency Medical Services in the Region Zealand and Capital Region of Denmark, and staff at the pharmacy of the Capital Region of Denmark.

Authors' contributions

JMM had full access to all of the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis. JMM, JL, LERO, TE, FF, LBA, and HCC were responsible for the concept and design. JMM and RPB did the statistical analysis. All authors took part in acquisition, analysis, and interpretation of data. JMM drafted the manuscript. All authors critically reviewed, read, and approved the manuscript.

Funding

Open access funding provided by Copenhagen University.
The study was supported by Novo Nordisk Foundation. The funders had no role in study.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Before initiation, the trial was registered at https://clinicaltrials.gov (Unique Identifer: NCT05462730) and approved in the Clinical Trials Information System (EU-CT number: 2022–500762-10–00) and by the Danish Data Protection Agency (ID: P-2022–280), and all patients provided informed consent.

Consent for publication

Not applicable.

Competing interests

T. Engstrøm has received speaker fees from Abbott Vascular, Boston Scientific, and Bayer, an advisory board fee from Abbott, Novo Nordisk and participated in Data Safety Monitoring of the INFINITY Trial, unrelated to this topic. C. Hassager has received an unrestricted grant from the Lundbeck Foundation, a speaker honorarium from Abiomed, and holds positions as a board member of the European Society of Cardiology. F. Folke has received research grants from the Novo Nordisk Foundation and the Laerdal Foundation. M. Minkkinen has received travel expenses and speaker fee from Abbott and speaker fee and proctoring for Boston Scientific. J. Lønborg has received an advisory board fee, an unrestricted grant, and speakers fee from Boston Scientific and speakers fee from Abbott, unrelated to this topic. All other au-thors have no conflicts of interest to disclose.

Author details

[1]Department of Cardiology, Rigshospitalet, Copenhagen University Hospital, Inge Lehmanns Vej 7, Copenhagen 2100, Denmark
[2]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark
[3]Copenhagen Emergency Medical Services, University of Copenhagen, Copenhagen, Denmark
[4]Department of Cardiology, Copenhagen University Hospital Herlev, Copenhagen, Denmark
[5]Region Zealand Emergency Medical Services, Naestved, Denmark

Received: 26 September 2024 / Accepted: 8 March 2025
Published online: 18 March 2025

References

1. Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, et al. 2023 ESC guidelines for the management of acute coronary syndromes. Eur Heart J. 2023;44:3720–826.
2. Konijnenberg LSF, Damman P, Duncker DJ, Kloner RA, Nijveldt R, van Geuns R-JM, et al. Pathophysiology and diagnosis of coronary microvascular dysfunction in ST-elevation myocardial infarction. Cardiovasc Res. 2020;116:787–805.
3. Symons R, Pontone G, Schwitter J, Francone M, Iglesias JF, Barison A, et al. Long-Term incremental prognostic value of cardiovascular magnetic resonance after ST-Segment elevation myocardial infarction. JACC Cardiovasc Imaging. 2018;11:813–25.
4. De Maria GL, Alkhalil M, Wolfrum M, Fahrni G, Borlotti A, Gaughran L, et al. Index of microcirculatory resistance as a tool to characterize microvascular obstruction and to predict infarct size regression in patients with STEMI undergoing primary PCI. JACC Cardiovasc Imaging. 2019;12:837–48.
5. Fearon WF, Balsam LB, Farouque HMO, Caffarelli AD, Robbins RC, Fitzgerald PJ, et al. Novel index for invasively assessing the coronary microcirculation. Circulation. 2003;107:3129–32.
6. Hausenloy DJ, Yellon DM. Myocardial ischemia-reperfusion injury: a neglected therapeutic target. J Clin Invest. 2013;123:92–100.
7. Francisco J, Del Re DP. Inflammation in myocardial ischemia/reperfusion injury: underlying mechanisms and therapeutic potential. Antioxidants. 2023;12:1944.
8. Matter MA, Paneni F, Libby P, Frantz S, Stähli BE, Templin C, et al. Inflammation in acute myocardial infarction: the good, the bad and the ugly. Eur Heart J. 2024;45:89–103.
9. Cain DW, Cidlowski JA. Immune regulation by glucocorticoids. Nat Rev Immunol. 2017;17:233–47.

10. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med. 2021;384:693–704.
11. Dequin P-F, Meziani F, Quenot J-P, Kamel T, Ricard J-D, Badie J, et al. Hydrocortisone in severe Community-Acquired pneumonia. N Engl J Med. 2023;388:1931–41.
12. Lee SR, Kim HK, Youm JB, Dizon LA, Song IS, Jeong SH, et al. Non-genomic effect of glucocorticoids on cardiovascular system. Pflugers Arch. 2012;464:549–59.
13. Madsen JM, Obling LER, Rytoft L, Folke F, Hassager C, Andersen LB, et al. Pre-hospital pulse glucocorticoid therapy in patients with ST-segment elevation myocardial infarction transferred for primary percutaneous coronary intervention: a randomized controlled trial (PULSE-MI). Trials. 2023;24:808.
14. Madsen JM, Engstrøm T, Obling LER, Zhou Y, Nepper-Christensen L, Beske RP et al. Prehospital Pulse-Dose glucocorticoid in ST-Segment elevation myocardial infarction: the PULSE-MI randomized clinical trial. JAMA Cardiol. 2024;9(10):882–91.
15. Pijls NHJ, De Bruyne B, Smith L, Aarnoudse W, Barbato E, Bartunek J, et al. Coronary thermodilution to assess flow reserve: validation in humans. Circulation. 2002;105:2482–6.
16. Jenista ER, Wendell DC, Azevedo CF, Klem I, Judd RM, Kim RJ, et al. Revisiting how we perform late gadolinium enhancement CMR: insights gleaned over 25 years of clinical practice. J Cardiovasc Magn Reson Off J Soc Cardiovasc Magn Reson. 2023;25:18.
17. van Kranenburg M, Magro M, Thiele H, de Waha S, Eitel I, Cochet A, et al. Prognostic value of microvascular obstruction and infarct size, as measured by CMR in STEMI patients. JACC Cardiovasc Imaging. 2014;7:930–9.
18. Liu T, Howarth AG, Chen Y, Nair AR, Yang H-J, Ren D, et al. Intramyocardial hemorrhage and the wave front of reperfusion injury compromising myocardial salvage. J Am Coll Cardiol. 2022;79:35–48.
19. Kandler D, Lücke C, Grothoff M, Andres C, Lehmkuhl L, Nitzsche S, et al. The relation between hypointense core, microvascular obstruction and intramyocardial haemorrhage in acute reperfused myocardial infarction assessed by cardiac magnetic resonance imaging. Eur Radiol. 2014;24:3277–88.
20. Scarsini R, Shanmuganathan M, De Maria GL, Borlotti A, Kotronias RA, Burrage MK, et al. Coronary microvascular dysfunction assessed by pressure wire and CMR after STEMI predicts Long-Term outcomes. JACC Cardiovasc Imaging. 2021;14:1948–59.
21. Ottens TH, Nijsten MW, Hofland J, Dieleman JM, Hoekstra M, van Dijk D, et al. Effect of high-dose dexamethasone on perioperative lactate levels and glucose control: a randomized controlled trial. Crit Care. 2015;19:41.
22. Jin H, Yun H, Ma J, Chen Z, Chang S, Ge M, et al. Assessment of the acute effects of glucocorticoid treatment on coronary microembolization using cine, first-pass perfusion, and delayed enhancement MRI. J Magn Reson Imaging. 2016;43:921–8.
23. Ghobrial M, Bawamia B, Cartlidge T, Spyridopoulos I, Kunadian V, Zaman A, et al. Microvascular obstruction in acute myocardial infarction, a potential therapeutic target. J Clin Med. 2023;12:5934.
24. Sezer M, Oflaz H, Gören T, Okçular I, Umman B, Nişanci Y, et al. Intracoronary streptokinase after primary percutaneous coronary intervention. N Engl J Med. 2007;356:1823–34.
25. van Leeuwen MAH, van der Hoeven NW, Janssens GN, Everaars H, Nap A, Lemkes JS, et al. Evaluation of microvascular injury in revascularized patients with ST-Segment–Elevation myocardial infarction treated with Ticagrelor versus Prasugrel. Circulation. 2019;139:636–46.
26. Wijnbergen I, van 't Veer M, Lammers J, Ubachs J, Pijls NHJ. Absolute coronary blood flow measurement and microvascular resistance in ST-elevation myocardial infarction in the acute and subacute phase. Cardiovasc Revascularization Med Mol Interv. 2016;17:81–7.
27. El Farissi M, Zimmermann FM, De Maria GL, van Royen N, van Leeuwen MAH, Carrick D, et al. The index of microcirculatory resistance after primary PCI: A pooled analysis of individual patient data. JACC Cardiovasc Interv. 2023;16:2383–92.

Publisher's Note