Impact of Morphine Treatment With and Without Metoclopramide Coadministration on Myocardial and Microvascular Injury in Acute Myocardial Infarction: Insights From the Randomized MonAMI Trial

Thomas Stiermaier, MD; Philipp Schaefer; Roza Meyer-Saraei, PhD; Mohammed Saad, MD; Suzanne de Waha-Thiele, MD; Janine Pöss, MD; Georg Fuernau, MD; Tobias Graf, MD; Thomas Kurz, MD; Alex Frydrychowicz, MD; Jörg Barkhausen, MD; Steffen Desch, MD; Holger Thiele, MD; Ingo Eitel, MD*

BACKGROUND: Intravenous morphine administration can adversely affect platelet inhibition induced by P2Y₁₂ receptor inhibitors after acute myocardial infarction. In contrast, some evidence suggests that opioid agonists may have cardioprotective effects on the myocardium. The aim of this prospective, randomized MonAMI (Impact of Morphine Treatment With and Without Metoclopramide Coadministration on Platelet Inhibition in Acute Myocardial Infarction) trial was, therefore, to investigate the impact of morphine with or without metoclopramide coadministration on myocardial and microvascular injury.

METHODS AND RESULTS: Patients with acute myocardial infarction (n=138) were assigned in a 1:1:1 ratio to ticagrelor 180 mg plus: (1) intravenous morphine 5 mg (morphine group); (2) intravenous morphine 5 mg and metoclopramide 10 mg (morphine+metoclopramide group); or (3) intravenous placebo (control group) administered before primary percutaneous coronary intervention. Cardiac magnetic resonance imaging was performed in 104 patients on day 1 to 4 after the index event. Infarct size was significantly smaller in the morphine only group as compared with controls (percentage of left ventricular mass, 15.5 versus 17.9; \( P = 0.047 \)). Furthermore, the number of patients with microvascular obstruction was significantly lower after morphine administration (28% versus 54%; \( P = 0.022 \)) and the extent of microvascular obstruction was smaller (percentage of left ventricular mass, 0 versus 0.74; \( P = 0.037 \)). In multivariable regression analysis, morphine administration was independently associated with a reduced risk for the occurrence of microvascular obstruction (odds ratio, 0.37; 95% CI, 0.14–0.93 [\( P = 0.035 \)]). There was no significant difference in infarct size (\( P = 0.491 \)) and extent (\( P = 0.753 \)) or presence (\( P = 0.914 \)) of microvascular obstruction when comparing the morphine+metoclopramide group with the control group.

CONCLUSIONS: In this randomized study, intravenous administration of morphine before primary percutaneous coronary intervention resulted in a significant reduction of myocardial and microvascular damage following acute myocardial infarction. This effect was not observed in the morphine plus metoclopramide group.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT02627950.

Key Words: infarct size ■ microvascular injury ■ morphine ■ myocardial infarction

Correspondence to: Ingo Eitel, MD, Medical Clinic II, University Heart Center Lübeck, University Hospital Schleswig-Holstein, Ratsbeuger Allee 160, 23538 Lübeck, Germany. E-mail: ingo.eitel@uksh.de

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*Dr Thiele and Dr Eitel are co-senior authors.

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Relief of pain and anxiety is of paramount importance in patients with acute myocardial infarction (AMI) to reduce the accompanying sympathetic activation, which causes vasoconstriction and increases cardiac workload. Therefore, current guidelines recommend titrated intravenous administration of opioids (eg, morphine) in case of persistent, severe chest pain (class IIa, level of evidence C).\(^1,2\)

However, the impact of morphine administration on myocardial damage and clinical outcome after AMI is subject of controversial debate. Morphine reduces intestinal motility, inhibits gastric emptying, and can induce nausea and vomiting.\(^3\) These side effects are associated with a slower uptake of orally administered P2Y\(_{12}\) receptor inhibitors, resulting in a delayed onset of effective antiplatelet therapy and potentially early treatment failure (eg, caused by stent thrombosis or incomplete microvascular reperfusion).\(^4-6\)

Coadministration of the prokinetic drug metoclopramide can attenuate the unintended gastrointestinal effects of morphine and preserve the pharmacokinetics and pharmacodynamics of P2Y\(_{12}\) receptor inhibitors.\(^7,8\)

In contrast to the adverse impact on platelet inhibition, some evidence suggests that opioids may be involved in cardioprotection against ischemia-reperfusion injury. Although the exact signaling pathways are incompletely understood, enhanced endogenous release of opioids into the systemic circulation has been proposed as a mechanism to translate cardioprotective stimuli to the heart.\(^9,10\)

Currently, available data regarding the effect of exogenous morphine administration on myocardial damage and clinical outcome are derived from methodologically limited nonrandomized studies with inconsistent results.\(^11-14\)

The aim of this randomized study was, therefore, to investigate the impact of morphine with and without metoclopramide coadministration on myocardial and microvascular injury after AMI assessed by cardiac magnetic resonance (CMR) imaging.

**CLINICAL PERSPECTIVE**

**What Is New?**
- In this randomized clinical trial that included 104 patients with acute myocardial infarction, intravenous administration of morphine before primary percutaneous coronary intervention resulted in a significant reduction of infarct size and microvascular obstruction assessed with cardiac magnetic resonance imaging.

**What Are the Clinical Implications?**
- Intravenous administration of morphine may have favorable, cardioprotective effects in patients with acute myocardial infarction, which, however, requires validation in adequately powered studies with clinical end points.

**Nonstandard Abbreviations and Acronyms**

| Abbreviation | Definition |
|--------------|------------|
| %LV          | Percentage of left ventricular mass |
| MonAMI       | Impact of Morphine Treatment With and Without Metoclopramide Coadministration on Platelet Inhibition in Acute Myocardial Infarction |
| MVO          | Microvascular obstruction |
| TIMI         | Thrombolysis in Myocardial Infarction |

**METHODS**

**Study Design and Patient Population**

The data that support the findings of this study are available from the corresponding author on reasonable request. We present a predefined substudy of the prospective, randomized, controlled, single-blind MonAMI (Impact of Morphine Treatment With and Without Metoclopramide Coadministration on Platelet Inhibition in Acute Myocardial Infarction) trial, which was conducted at the University Heart Center Lübeck between December 2015 and October 2018. The detailed study protocol has been previously published.\(^6\) In brief, 138 patients with AMI according to the third universal definition of myocardial infarction and persistent chest pain were assigned in a 1:1:1 ratio to loading with ticagrelor 180 mg and intravenous administration of: (1) NaCl (placebo [control] group); (2) morphine 5 mg (morphine group); or (3) morphine 5 mg plus metoclopramide 10 mg (morphine+metoclopramide group). All study drugs were administered before primary percutaneous coronary intervention (PCI). Randomization was performed with sealed, unlabeled envelopes and computer-generated, random numbers stratified by ST-segment–elevation myocardial infarction (STEMI) and non-STEMI (NSTEMI). Patients but not the interventional cardiologists were blinded to the allocated treatment group. The main exclusion criteria were as follows: age <18 years; active bleeding or bleeding diathesis; history of intracranial hemorrhage; current oral anticoagulation or treatment with clopidogrel, ticagrelor, or prasugrel; glycoprotein IIb/IIIa inhibitors, morphine, and/or metoclopramide <12 hours; fibrinolysis <48 hours; PCI or coronary artery bypass grafting <3 months; contraindications to antiplatelet
therapy; known liver dysfunction or glomerular filtration rate <30 mL/min; pregnancy or breast feeding; and participation in another trial.

The primary end point of the MonAMI trial, P2Y<sub>12</sub> reactivity units 2 hours after ticagrelor loading, showed significantly higher platelet reactivity in the morphine compared with the control group, whereas this adverse effect was reversed in the morphine+metoclopramide group.<sup>5</sup>

The study was conducted according to Good Clinical Practice and the Helsinki Declaration. The protocol was approved by the local ethics committee and registered at ClinicalTrials.gov (identifier: NCT02627950). All patients gave written informed consent.

**Primary PCI and Medical Treatment**

Primary PCI was performed within 24 hours after symptom onset according to standard clinical practice and guideline recommendations with stenting of the culprit lesion in case of a vessel diameter >2 mm using drug-eluting stents. In patients with multivessel coronary artery disease, the treatment strategy of nonculprit lesions was planned by the operator considering clinical patient characteristics, angiographic criteria, and practice guidelines (immediate multivessel PCI versus staged revascularization with or without hemodynamic assessment). Aspiration thrombectomy or administration of glycoprotein IIb/IIIa inhibitors in bailout situations was left to the operators’ discretion. Intracoronary imaging with intravascular ultrasound or optical coherence tomography was not performed routinely. All patients received aspirin 500 mg intravenously and ticagrelor 180 mg orally before PCI and periprocedural anticoagulation with unfractionated heparin (targeted activated clotting time >250 seconds). Subsequent antiplatelet therapy included ticagrelor 90 mg BID for at least 12 months and aspirin 100 mg indefinitely. Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, β-blockers, and statins were strongly recommended according to guidelines.

**CMR Imaging**

CMR imaging was performed in patients without contraindications on day 1 to 4 after the index event on a clinical 1.5 Tesla magnetic resonance scanner. The standardized postinfarction imaging protocol has been previously described and included balanced steady-state free precession images for the assessment of left ventricular volumes and function and T1-weighted inversion recovery turbo gradient echo sequences about 15 minutes after intravenous administration of a gadolinium-based contrast agent (gadobutrol 0.2 mmol/kg body weight, late gadolinium enhancement imaging) to determine infarct size and microvascular obstruction (MVO).<sup>15</sup> Furthermore, T2-weighted short tau inversion recovery sequences were used to visualize myocardial edema, which allowed the differentiation between acute and chronic infarction.

Images were analyzed offline in a core laboratory at the University Heart Center Lübeck by blinded investigators. Continuous short-axis slices covering the whole left ventricle from base to apex were used to assess CMR parameters with certified evaluation software (cmr42, Circle Cardiovascular Imaging Inc.). Regions of infarcted myocardium and MVO were delineated with semiautomated computer-aided threshold detection (>5 SDs of remote myocardium in ≥10 adjacent pixels) and expressed as percentage of left ventricular mass (%LV). MVO was defined as the core area of nonenhancement within the infarcted myocardium. If present, MVO was included in the overall infarct size and quantified separately. The core laboratory has proven excellent reproducibility and low interobserver and intraobserver variability.<sup>15</sup>

**Statistical Analysis**

Categorical variables are presented as numbers and percentage of patients and were compared with chi-square test. The majority of continuous variables were nonnormally distributed in Shapiro-Wilk testing and are therefore expressed as median with interquartile range. Between-group differences were assessed with the nonparametric Mann-Whitney U test comparing the morphine arms separately with the control group. Baseline characteristics were compared between patients with CMR imaging, who were included in the study, and patients not included in the study because of missing CMR data. The placebo group was compared with the morphine only and the morphine+metoclopramide groups regarding differences in CMR imaging results. Furthermore, predictors of MVO were assessed in univariate and stepwise multivariable logistic regression analysis including all baseline clinical and procedural characteristics. Only significant variables in univariate analysis were included in multivariable testing. Results are presented as odds ratios (with 95% CIs). Regression analysis was also performed in the subgroup of patients with STEMI.

All analyses were performed with SPSS version 23.0 (IBM). A 2-tailed P<0.05 was considered statistically significant.

**RESULTS**

Of 340 consecutive patients with AMI, 138 patients (STEMI, n=94; NSTEMI, n=44) were randomized in the MonAMI trial. Excluding patients with no or incomplete CMR data (n=34; 24.6%) because of refused consent for CMR (n=10), claustrophobia (n=9), metallic implants (n=6), death or severe comorbidity of a gadolinium-based contrast agent (gadobutrol 0.2 mmol/kg body weight, late gadolinium enhancement imaging) to determine infarct size and microvascular obstruction (MVO).<sup>15</sup> Furthermore, T2-weighted

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(n=5), or early termination of the scan (n=4), the final population for the present substudy comprised 104 patients (Figure 1). Baseline clinical and procedural characteristics were similar between patients included in the present study and patients without CMR imaging except for a more severely impaired Thrombolysis in Myocardial Infarction (TIMI) flow grade post-PCI in excluded patients (P=0.037; Tables S1 and S2).

**Clinical and Procedural Characteristics**

The patient population was predominantly male with a median age of 64 years (interquartile range, 55–74 years) and a typical cardiovascular risk profile for patients with AMI. About two thirds of patients had STEMI and the left anterior descending coronary artery was the culprit vessel in half of the study participants. All patients were treated with drug-eluting stent implantation, preceded by a predilatation in 72% of cases. TIMI flow grade 3 was achieved in 91% of patients. Baseline clinical and procedural characteristics according to the randomized study arms are illustrated in Tables 1 and 2. There were no significant differences between the placebo group and the respective treatment arms except for a higher number of patients with immediate multivessel PCI in the morphine+metoclopramide group (P=0.049).

**CMR Results**

The median time from AMI to CMR was 3 days (interquartile range, 2–4 days) without significant differences between the study groups. Infarct size (15.5%LV versus 17.9%LV; P=0.047) and the extent of MVO (0%LV versus 0.74%LV; P=0.037) were significantly smaller in the morphine only compared with the control group (Table 3; Figure 2). Furthermore, the number of patients with MVO was significantly lower after morphine administration (28% versus 54%; P=0.022). Left ventricular ejection fraction did not differ significantly between the groups (P=0.970). Comparison of the morphine+metoclopramide with the control group did not result in significant differences regarding left ventricular ejection fraction (P=0.790), infarct size (P=0.491), and extent (P=0.753) or presence (P=0.914) of MVO (Table 3; Figure 2).

Multivariable regression analysis identified the administration of morphine only as a protective factor for the occurrence of MVO (odds ratio, 0.37; 95% CI, 0.14–0.93 (P=0.035)) (Table 4). The presence of STEMI was the only additional marker that was independently associated with microvascular injury. When considering only the smaller subgroup of patients with STEMI, the effect of morphine on MVO did not reach statistical significance in regression analysis (P=0.195).

**DISCUSSION**

The main findings of this randomized trial in patients with AMI are that morphine administration significantly reduced myocardial and microvascular injury and was independently associated with a reduced risk for the occurrence of MVO. In contrast, the combined administration of morphine+metoclopramide did not have a significant effect on infarct size or MVO compared with placebo.

Real-world data show that more than half of patients with AMI receive intravenous morphine to relieve pain and attenuate sympathetic activation. This approach is consistent with current guidelines, which recommend intravenous opioids as the analgetics of choice in symptomatic patients, albeit with a decreasing strength of recommendation (class I, level C in 2012 to class IIa, level C in 2017). A major concern is that morphine may slow intestinal absorption of oral platelet inhibitors with a subsequently increased risk of stent thrombosis and adverse clinical outcome. A slower uptake of P2Y$_{12}$ receptor inhibitors after morphine administration, which results in a delayed onset of effective platelet inhibition, has been shown in several previous trials. Most recently, the randomized MonAMI trial confirmed these morphine-induced side effects and further suggests that co-administration of metoclopramide can preserve the pharmacokinetics and pharmadynamics of P2Y$_{12}$ receptor inhibitors. However, it is still unclear whether
the impact on platelet inhibition translates into an increased risk of clinical events in patients receiving morphine. Adequately powered, randomized trials with clinical end points are lacking and data from studies with considerable methodological limitations provide inconsistent results.13,17–19 In the absence of robust evidence regarding clinical events, the use of CMR imaging provides valuable mechanistic insights into the effect of morphine on myocardial and microvascular damage, which are established surrogate markers for the risk of adverse clinical outcome.15,20 Previous nonrandomized studies in patients with STEMI showed inconsistent results. While one analysis in 276 patients reported suboptimal reperfusion success (larger infarct size, higher extent of MVO, and less myocardial salvage) after morphine

| Variable | Placebo (n=39) | Morphine (n=36) | Morphine+Metoclopramide (n=29) | Placebo vs Morphine | Placebo vs Morphine+Metoclopramide |
|----------|---------------|----------------|-------------------------------|---------------------|-----------------------------------|
| Age, y   | 68 (56–76)    | 62 (55–74)    | 60 (51–73)                   | 0.518               | 0.163                             |
| Women    | 12/39 (31%)   | 11/36 (31%)   | 6/29 (21%)                   | 0.984               | 0.351                             |
| Current smoking | 17/39 (44%) | 16/36 (44%) | 12/29 (41%) | 0.941 | 0.855 |
| Hypertension | 26/39 (67%) | 22/36 (61%) | 20/29 (69%) | 0.617 | 0.841 |
| Hypercholesterolemia | 13/39 (33%) | 8/36 (22%) | 9/29 (31%) | 0.284 | 0.841 |
| Diabetes mellitus | 6/39 (15%) | 9/36 (25%) | 8/29 (28%) | 0.298 | 0.218 |
| Body mass index, kg/m² | 27 (25–31) | 27 (24–33) | 28 (25–31) | 0.414 | 0.766 |
| Systolic blood pressure, mm Hg | 139 (125–151) | 130 (120–160) | 130 (120–154) | 0.482 | 0.311 |
| Diastolic blood pressure, mm Hg | 80 (70–90) | 80 (70–93) | 80 (70–92) | 0.935 | 0.541 |
| Heart rate, beats per min | 80 (70–103) | 76 (65–95) | 80 (60–90) | 0.232 | 0.258 |
| Previous myocardial infarction | 5/39 (13%) | 2/36 (6%) | 4/29 (14%) | 0.280 | 0.907 |
| Previous PCI | 7/39 (18%) | 3/36 (8%) | 5/29 (17%) | 0.221 | 0.940 |
| Previous CABG | 1/39 (3%) | ... | ... | 0.333 | 0.385 |
| Previous stroke | 1/39 (3%) | 2/36 (6%) | 3/29 (10%) | 0.509 | 0.177 |
| Peripheral vascular disease | 2/39 (5%) | 1/36 (3%) | 1/29 (3%) | 0.604 | 0.739 |
| GRACE score | 120 (96–136) | 107 (92–125) | 111 (88–125) | 0.304 | 0.256 |
| Pain-to-balloon time, min | 284 (148–730) | 240 (137–777) | 288 (197–670) | 0.876 | 0.802 |
| Killip class on admission | | | | | |
| 1 | 36/39 (92%) | 32/36 (89%) | 25/29 (86%) | 0.478 | 0.351 |
| 2 | 2/39 (5%) | 4/36 (11%) | 2/29 (7%) | 0.984 | 0.351 |
| 3 | ... | ... | 1/29 (3%) | 0.672 | 0.672 |
| 4 | 1/39 (3%) | ... | 1/29 (3%) | 0.730 | 0.833 |
| Troponin T on admission, ng/L | 277 (70–647) | 168 (72–512) | 177 (31–1755) | 0.577 | 0.741 |
| Maximum troponin T, ng/L | 1523 (828–4337) | 174 (960–3071) | 2214 (1441–6193) | 0.936 | 0.224 |
| CK-MB on admission, U/L | 52.4 (23.3–81.6) | 62.6 (44.7–113.5) | 55.8 (41.0–211.5) | 0.084 | 0.329 |
| Maximum CK-MB, U/L | 70.7 (32.4–107.8) | 74.1 (36.6–119.0) | 64.5 (34.3–202.3) | 0.730 | 0.833 |

Data are presented as n/N (percentage) or median (interquartile range). CABG indicates coronary artery bypass graft; CK-MB, creatine kinase myocardial band; GRACE, Global Registry of Acute Coronary Events; NSTEMI, non–ST-segment-elevation myocardial infarction; PCI, percutaneous coronary intervention; and STEMI, ST-segment-elevation myocardial infarction.
administration, a more recent study did not reveal a negative impact of morphine on myocardial damage in 734 patients with STEMI. In contrast, the latter trial suggested a potential cardioprotective effect of morphine in patients with a reduced flow in the culprit vessel (TIMI flow ≤2) and early reperfusion within 120 minutes (smaller infarct size, reduced MVO). To the best of our knowledge, the present study is the first to investigate the impact of morphine administration on myocardial damage in patients with STEMI and NSTEMI with a randomized design. The results indicate a significantly reduced myocardial and microvascular damage in the morphine compared with the placebo group. At first, this finding seems confusing since distal embolization of thrombotic material is one mechanism of microvascular injury that might aggravate in case of delayed onset of effective platelet inhibition. However, MVO is a multifactorial process that includes ischemia-reperfusion injury, tissue inflammation, and endothelial dysfunction in addition to distal embolization. Our results imply that thrombotic material is not the pivotal factor for microvascular injury or that the effect of P2Y12 inhibitors is not sufficient to prevent distal embolization and MVO. Opioids have been associated with favorable cardioprotective effects on the myocardium, which might explain our findings. Remote ischemic conditioning is an interesting approach to reduce myocardial damage, although the promising findings in experimental models did not consistently result in a reduction of adverse events following AMI in clinical trials. Enhanced endogenous release of opioids has been proposed as a key mechanism to confer protection against ischemia-reperfusion injury and translate conditioning stimuli from various organs to the heart. A definite proof that exogenous administration of opioids can induce similar protective effects is currently lacking. Nevertheless,
intravenous morphine targets the same opioid receptors involved in the transmission of cardioprotective stimuli. Furthermore, the attenuated sympathetic drive after morphine administration prevents vasoconstriction and decreases cardiac workload associated with tachycardia and/or hypertension and might consequently limit myocardial damage after AMI. Interestingly, we did not observe reduced myocardial and microvascular injury in the morphine+metoclopramide group. A potential drug interaction between intravenously administered morphine and metoclopramide cannot be completely excluded but seems unlikely. Differences in baseline characteristics are the more likely explanation for our findings. Despite being a randomized trial, the morphine+metoclopramide arm of the CMR substudy included a higher proportion of patients with STEMI and a more severely impaired TIMI flow pre-PCI compared with the other study arms, albeit statistically not significant. This factor has likely balanced the potential protective effects of morphine and leads to the limitations of the present study. The MonAMI trial was not designed to assess differences in CMR imaging parameters of myocardial injury, and the power calculation was based on its primary end point, P2Y12 reactivity units measured by the VerifyNow P2Y12 test. Furthermore, contraindications for CMR imaging were not a priori an exclusion criterion for study participation, which led to a comparatively high CMR dropout rate in the current analysis and the differences in baseline characteristics despite randomization. The small sample size did not allow more detailed analyses regarding the effects of morphine in certain subgroups and multiple testing corrections were not performed. The optimal time point of postinfarction CMR imaging to assess myocardial and microvascular damage is a matter of debate. Nevertheless, the timeframe in our study is in line with previous large CMR studies and consensus recommendations. Other limitations are the single-center design and the inclusion of

| Variable | Placebo (n=39) | Morphine (n=36) | Morphine+Metoclopramide (n=29) | Placebo vs Morphine | Placebo vs Morphine+Metoclopramide |
|----------|---------------|----------------|-----------------------------|---------------------|----------------------------------|
| LV ejection fraction, % | 54 (42 to 57) | 52 (43 to 57) | 51 (41 to 58) | 0 (−4 to 6) | 0.970 | −1 (−7 to 4) | 0.790 |
| LV end-diastolic volume, mL | 143 (127 to 172) | 144 (121 to 181) | 148 (134 to 180) | −2 (−20 to 16) | 0.820 | 7 (−12 to 25) | 0.464 |
| LV end-systolic volume, mL | 69 (58 to 96) | 72 (52 to 97) | 76 (56 to 93) | −1 (−16 to 13) | 0.890 | 4 (−10 to 18) | 0.602 |
| Infarct size, %LV | 17.9 (12.3 to 32.9) | 15.5 (5.0 to 21.4) | 23.7 (11.3 to 37.2) | −5.9 (−12.3 to −0.4) | 0.047 | 3.0 (−5.2 to 11.2) | 0.491 |
| MVO | 21/39 (54%) | 10/36 (28%) | 16/29 (55%) | ... | 0.022 | ... | 0.914 |
| MVO, %LV | 0.74 (0 to 3.10) | 0 (0 to 1.40) | 0.76 (0 to 1.85) | 0 (−0.9 to 0) | 0.037 | 0 (−0.8 to 0) | 0.753 |

Data are presented as n/N (percentage) and median (interquartile range). %LV indicates percentage of left ventricular mass; CMR indicates cardiac magnetic resonance; LV, left ventricular; MVO, microvascular obstruction.

*Hodges-Lehman median difference with 95% CI.

Figure 2. Infarct size and microvascular obstruction (MVO).
Infarct size (A) and MVO (B) according to the randomized treatment groups. %LV indicates percentage of left ventricular mass.
patients with STEMI and those with NSTEMI, causing heterogeneity of the study population resulting in a possible reduced statistical power of this analysis. In view of these limitations, the results of our trial have to be considered as hypothesis generating and require validation in future investigations.

CONCLUSIONS

In this randomized trial, intravenous administration of morphine before primary PCI resulted in a significant reduction of myocardial and microvascular damage following AMI. In contrast, this effect was not observed in patients receiving morphine with coadministration of metoclopramide. A potential cardioprotective effect of morphine requires further evaluation in well-designed future trials with clinical end points and adequate sample sizes.

ARTICLE INFORMATION

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Affiliations

From the Medical Clinic II, University Heart Center Lübeck, Lübeck, Germany (T.S., P.S., R.M., M.S., S.d.W., G.F., T.G., T.K., I.E.); German Center for Cardiovascular Research (DZHK), Partner Site Hamburg/Kiel/Lübeck, Lübeck, Germany (T.S., P.S., R.M., M.S., S.d.W., G.F., T.G., T.K., I.E.); Department of Internal Medicine/Cardiology and Leipzig Heart Institute, Heart Center Leipzig at University of Leipzig, Germany (J.P., S.D., H.T.); and Department of Radiology and Nuclear Medicine, University Hospital Schleswig-Holstein, Lübeck, Germany (A.F., J.B.).

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Disclosures

None.

Supplementary Material

Tables S1–S2

REFERENCES

1. Ibáñez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Cañamero AL, Crea F, Goudevanov JA, Halvorsen S, et al. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018;39:119–177. DOI: 10.1093/eurheartj/ehy393.

2. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigi M, Andreotti F, Bax JJ, Borger MA, Bretscher C, Chew DP, et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting Without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J. 2016;37:267–315. DOI: 10.1093/eurheartj/ehv320.

3. Nimmo WS, Wilson J, Prescott LF. Narcotic analgesics and delayed gastric emptying during labour. Lancet. 1975;1:890–893. DOI: 10.1016/ S0140-6736(75)91687-6.

4. Kubicza J, Adamski P, Ostrowska M, Sikora J, Kubicza JM, Skora WD, Stanekowska K, Buszko K, Navarese EP, Jilma B, et al. Morphine delays and attenuates ticagrelor exposure and action in patients with myocardial infarction: the randomized, double-blind, placebo-controlled IMPRESSION trial. Eur Heart J. 2016;37:245–252. DOI: 10.1093/eurheartj/ehv547.

5. Parodi G, Bellandi B, Xanthopoulou I, Capranzano P, Capodanno D, Valenti R, Stavrou K, Migliorini A, Antoniucci D, Tamburino C, et al. Morphine is associated with a delayed activity of oral antiplatelet agents in patients with ST-elevation acute myocardial infarction undergoing primary percutaneous coronary intervention. Circ Cardiovasc Interv. 2014;8:e001593. DOI: 10.1161/CIRCINTERVENTIONS.114.001593.

6. Silvain J, Storey RF, Cayla G, Esteve J-B, Dillinger JG, Rousseau H, Marchionni N, Alexopoulos D, Parodi G. Morphine use and myocardial reperfusion in patients with acute myocardial infarction: the randomized, double-blind, placebo-controlled METAMORPHOSIS Trial. Thromb Haemost. 2016;116:369–378. DOI: 10.1160/TH15-12-0944.

7. Sikora J, Neizgoda P, Barańska M, Buszko K, Skibirska N, Skora W, Pstrągowski K, Siller-Matula J, Bernd J, Gorog D, et al. Metoclopramide Administration as a Strategy to Overcome Morphine-Ticagrelor Interaction in Patients With Unstable Angina Pectoris—the METAMORPHOSIS Trial. Thromb Haemost. 2018;111:2126–2133. DOI: 10.1160/TH18-03-0383.

8. Saad M, Meyer-Saraei R, de Waha-Thiele S, Stiermaier T, Graf T, Fuernau G, Langer HF, Kurz T, Füss J, Barkausen J, et al. Impact of morphine treatment with and without metoclopramide coadministration on ticagrelor induced platelet inhibition in acute myocardial infarction—the randomized MonAMI trial. Circulation. 2020;141:1354–1356. DOI: 10.1161/CIRCULATIONAHA.119.042816.

9. Randhawa PK, Jaggi AS. Opioids in remote ischemic preconditioning-induced cardioprotection. J Cardiovasc Pharmacol Ther. 2017;22:112–121. DOI: 10.1177/1074248X16660921.

10. Rentoukas I, Giannopoulos G, Kaoakis A, Kossyvakis C, Raisakis K, Driva M, Panagopoulou I, Tsarouchas K, Vavetsi S, Pyrgakis V, et al. Cardioprotective role of remote ischemic perconditioning in primary percutaneous coronary intervention: enhancement by opioid action. JACC Cardiovasc Interv. 2010;3:49–55. DOI: 10.1016/j.jcin.2009.10.015.

11. de Waha S, Ittel I, Desch S, Fuernau G, Lurz P, Urban D, Schulzer G, Thiele H. Intravenous morphine administration and reperfusion success in ST-elevation myocardial infarction: insights from cardiac magnetic resonance imaging. Clin Res Cardiol. 2015;104:727–734. DOI: 10.1007/s00392-015-0835-2.

12. Bellandi B, Zocchi C, Xanthopoulou I, Scudiero F, Valenti R, Migliorini A, Antoniucci D, Marchionni N, Alexopoulos D, Parodi G. Morphine use and myocardial reperfusion in patients with acute myocardial
Supplemental Material
### Table S1. Baseline characteristics included versus excluded patients.

| Variable                                      | Included (n=104) | Excluded (n=34) | p     |
|-----------------------------------------------|------------------|-----------------|-------|
| Age, years                                    | 64 (55, 74)      | 65 (58, 75)     | 0.756 |
| Female sex                                    | 29/104 (28%)     | 9/34 (27%)      | 0.873 |
| **Cardiovascular risk factors**               |                  |                 |       |
| Current Smoking                               | 45/104 (43%)     | 18/34 (53%)     | 0.326 |
| Hypertension                                  | 68/104 (65%)     | 19/34 (56%)     | 0.319 |
| Hypercholesterolemia                          | 30/104 (29%)     | 11/34 (32%)     | 0.698 |
| Diabetes mellitus                             | 23/104 (22%)     | 8/34 (24%)      | 0.864 |
| Body mass index, kg/m²                        | 27 (25, 31)      | 30 (26, 32)     | 0.033 |
| Systolic blood pressure, mmHg                 | 135 (120, 153)   | 130 (111, 149)  | 0.331 |
| Diastolic blood pressure, mmHg                | 80 (70, 90)      | 70 (60, 80)     | 0.008 |
| Heart rate, beats per minute                  | 80 (66, 95)      | 75 (69, 85)     | 0.169 |
| Previous myocardial infarction                | 11/104 (11%)     | 6/34 (18%)      | 0.276 |
| Previous PCI                                  | 15/104 (14%)     | 9/34 (27%)      | 0.108 |
| Previous CABG                                 | 1/104 (1%)       | 1/34 (3%)       | 0.402 |
| Previous stroke                               | 6/104 (6%)       | 1/34 (3%)       | 0.514 |
| Peripheral vascular disease                   | 4/104 (4%)       | 2/34 (6%)       | 0.613 |
| **Diagnosis**                                 |                  |                 | 0.623 |
| STEMI                                         | 72/104 (69%)     | 22/34 (65%)     |       |
| NSTEMI                                        | 32/104 (31%)     | 12/34 (35%)     |       |
| GRACE score                                   | 112 (94, 129)    | 112 (97, 129)   | 0.931 |
| Pain-to-balloon time, min                     | 276 (150, 711)   | 234 (147, 1191) | 0.644 |
| Killip class on admission                     |                  |                 | 0.804 |
| 1                                             | 93/104 (89%)     | 29/34 (85%)     |       |
| 2                                             | 8/104 (8%)       | 4/34 (12%)      |       |
| 3                                             | 1/104 (1%)       | -               |       |
| 4                                             | 2/104 (2%)       | 1/34 (3%)       |       |
| Troponin T on admission, ng/l                 | 192 (64, 577)    | 321 (52, 1485)  | 0.329 |
| Maximum Troponin T, ng/l                      | 1749 (1158, 3912)| 1514 (450, 4324)| 0.278 |
| CK-MB on admission, U/l                       | 59.4 (40.6, 107.5)| 90.3 (41.1, 226.0)| 0.371 |
| Maximum CK-MB, U/l                            | 72.5 (33.4, 109.0)| 50.8 (36.5, 125.4)| 0.636 |

Data are presented as n/N (%) and median (interquartile range).

CABG = coronary artery bypass graft; CK-MB = creatine kinase myocardial band; GRACE = Global Registry of Acute Coronary Events; MCP = metoclopramide; NSTEMI = Non-ST-elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-elevation myocardial infarction.
Table S2. Procedural characteristics included versus excluded patients.

| Variable                              | Included (n=104) | Excluded (n=34) | p   |
|---------------------------------------|------------------|-----------------|-----|
| Radial access                         | 72/104 (69%)     | 19/34 (56%)     | 0.154 |
| Procedural time, min                   | 50 (38, 61)      | 62 (39, 74)     | 0.146 |
| Fluoroscopic time, min                 | 10 (8, 16)       | 14 (9, 23)      | 0.173 |
| Contrast medium, ml                    | 200 (140, 273)   | 235 (150, 300)  | 0.251 |
| Vessel disease                         |                  |                 | 0.824 |
| 1                                     | 38/104 (37%)     | 11/34 (32%)     |     |
| 2                                     | 35/104 (34%)     | 11/34 (32%)     |     |
| 3                                     | 31/104 (30%)     | 12/34 (35%)     |     |
| Culprit vessel                         |                  |                 | 0.836 |
| Left anterior descending               | 50/104 (48%)     | 18/34 (53%)     |     |
| Left circumflex                        | 21/104 (20%)     | 7/34 (21%)      |     |
| Right coronary artery                  | 33/104 (32%)     | 9/34 (27%)      |     |
| Predilatation                          | 75/104 (72%)     | 24/34 (71%)     | 0.864 |
| Number of stents                       | 2 (1, 3)         | 1 (1, 2)        | 0.187 |
| Multivessel PCI                        | 13/104 (13%)     | 4/34 (12%)      | 0.910 |
| Glycoprotein IIb/IIla antagonists      | 8/104 (8%)       | 3/34 (9%)       | 0.833 |
| TIMI flow grade before PCI             |                  |                 | 0.971 |
| 0                                     | 52/104 (50%)     | 18/34 (53%)     |     |
| 1                                     | 11/104 (11%)     | 4/34 (11%)      |     |
| 2                                     | 19/104 (18%)     | 6/34 (18%)      |     |
| 3                                     | 22/104 (21%)     | 6/34 (21%)      |     |
| TIMI flow grade post PCI               |                  |                 | 0.037 |
| 0                                     | -                | 2/34 (6%)       |     |
| 1                                     | 4/104 (4%)       | 1/34 (3%)       |     |
| 2                                     | 5/104 (5%)       | 4/34 (12%)      |     |
| 3                                     | 95/104 (91%)     | 27/34 (79%)     |     |

Data are presented as n/N (%) and median (interquartile range).

MCP = metoclopramide; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction.