# Morphine analgesia pre-PPCI is associated with pro-thrombotic state, reduced spontaneous reperfusion and greater infarct size

Short title: Morphine impairs reperfusion pre-PPCI

Mohamed Farag, MSc[1,2], Nikolaos Spinthakis, MBBS[1,2], Manivannan Srinivasan, MD[2], Keith Sullivan, PhD[1], David Wellsted, PhD[1], Diana A Gorog, MD, PhD[1,2,3]

1. Postgraduate Medical School, University of Hertfordshire, UK
2. Department of Cardiology, East and North Hertfordshire NHS Trust, Hertfordshire, UK
3. National Heart & Lung Institute, Imperial College, London, UK

*Correspondence to:*

Prof. Diana A Gorog

National Heart and Lung Institute

Imperial College

Dovehouse Street, London SW3 6LR

United Kingdom

Tel +44 (0)207 034 8934

Fax +44 (0)207 034 8935

d.gorog@imperial.ac.uk

## Summary

The emergency management of ST-elevation myocardial infarction (STEMI) involves treatment with dual antiplatelet therapy (DAPT) and primary percutaneous coronary intervention (PPCI). Pain is generally treated with opiates, which may delay gastric transit, and reduce DAPT absorption. We sought to assess the effect of morphine on reperfusion, infarct size and thrombotic status in 300 patients presenting for PPCI. Morphine was given in a non-randomized fashion as required by emergency teams *en route* to the heart attack centre. All patients received DAPT and PPCI according to standard care, with optional glycoprotein IIb/IIIa inhibitor (GPI) use. Patients were assessed for ST-segment resolution, coronary flow, thrombotic status and peak troponin. Patients receiving morphine (n=218; 72.7%) experienced less spontaneous ST-segment resolution pre-PPCI, lower rate of TIMI 2/3 flow in the infarct-related artery pre-PPCI, and higher peak troponin level post-PPCI (median[IQR]; 1906[1002-4398] vs. 1268[249-2920] ng/L; p=0.016) than those who did not. Patients receiving morphine exhibited significantly enhanced platelet reactivity and impaired endogenous fibrinolysis on arrival, compared to no-morphine patients. Morphine administration was an independent predictor of failure of spontaneous ST-segment resolution after adjustment for other variables (OR 0.26; CI:0.08-0.84; p=0.025). Among patients receiving GPI, there was no difference in pre-PPCI flow or peak troponin according to morphine use, suggesting that the adverse effects of morphine relate to delayed DAPT absorption, that may be overcome by GPI. Our hypothesis-generating data suggest that morphine use in STEMI is associated with enhanced platelet reactivity, reduced spontaneous myocardial reperfusion (pre-PPCI) and larger infarct size, and these adverse effects may be influenced by GPI use.

**Clinical Trial Registration—**URL: http://www.clinicaltrials.gov. Unique identifier: NCT02562690

**Keywords:** opiates, morphine, percutaneous coronary intervention, thrombosis, endogenous fibrinolysis

## What is known about this topic?

• Opiate analgesia with morphine is frequently used to treat the symptoms of chest pain and related sympathetic activation in patients with ST-elevation myocardial infarction.

• The early administration of oral antiplatelet agents upstream of angiographic assessment and PPCI, is recommended by guidelines to improve clinical outcomes.

• Morphine administration reduces the onset and the antiplatelet effect of orally-administered $P2Y_{12}$ inhibitors, but whether this affects clinical outcomes is not clear.

## What does this paper add?

• In the largest study to-date examining the effects of morphine in patients with STEMI undergoing PPCI, morphine use was associated with both enhanced platelet reactivity and with impaired endogenous fibrinolysis.

• Morphine use was associated with reduced occurrence of spontaneous coronary reperfusion pre-PPCI and non-independently associated with larger infarct size.

• The adverse effects of morphine in patients with STEMI may be favourably influenced by upfront GPI administration.

## Abbreviations

ACS = acute coronary syndrome

HAC = heart attack centre

DAPT = dual antiplatelet medication

GPI = glycoprotein IIb/IIIa inhibitor

GTT = global thrombosis test

LT = lysis time

OT = occlusion time

PPCI = primary percutaneous coronary intervention

STEMI = ST-elevation myocardial infarction

TIMI = Thrombolysis in Myocardial Infarction

# Introduction

The emergency management of ST-elevation myocardial infarction (STEMI) involves the administration of dual antiplatelet medication (DAPT) and revascularization with primary percutaneous coronary intervention (PPCI). Guidelines recommend analgesia for the relief of pain and to reduce associated sympathetic activation (1). Conventionally, morphine or diamorphine is used, which may delay gastric transit, and reduce absorption of DAPT.

Pharmacodynamic and pharmacokinetic studies have shown that morphine use decreases the concentration and effects of $P2Y_{12}$ inhibitors (2), and is associated with reduced platelet inhibition (3-5). In a crossover study of 11 patients, coadministration of morphine delayed the onset of prasugrel's antiplatelet effect (6). In a pre-specified substudy of the ATLANTIC trial in 37 patients undergoing PPCI, morphine delayed the onset of action of ticagrelor as measured by vasodilator-associated stimulated phosphoprotein (VASP) platelet reactivity index and VerifyNow (7). In 300 patients with STEMI receiving prasugrel or ticagrelor, morphine administration was an independent predictor of high residual platelet reactivity 2 hours post-PPCI (8).

The MOJITO study showed that administration of ticagrelor in crushed form in STEMI patients achieved earlier platelet inhibition than whole tablets, but even in this group, morphine use was associated with higher on-treatment platelet reactivity (9). In the IMPRESSION trial, 70 patients with acute coronary syndrome (ACS; namely STEMI or non STEMI) were randomised to receive intravenous morphine or placebo followed by 180mg ticagrelor. Platelet reactivity was assessed with VASP, multiple electrode aggregometry and VerifyNow. All 3 tests showed that morphine delayed and attenuated the effect of ticagrelor (4). In 182 patients undergoing PPCI, of whom 72 received morphine, morphine use was associated with higher residual platelet reactivity measured by VerifyNow and reduced myocardial reperfusion post-PPCI. However, independent predictors of impaired myocardial

reperfusion *after* PCI were high residual platelet reactivity and TIMI flow grade after PPCI but not morphine use, questioning the direct relationship between morphine and reduced myocardial reperfusion (3).

Thus, the relationship between morphine use, myocardial reperfusion and infarct size remains contentious, at least in part due to the small size of prior studies. We sought to assess thrombotic status of STEMI patients undergoing PPCI, according to morphine use and relate this to coronary reperfusion, infarct size and clinical outcome.

# Methods

## Study design and population

We performed a prospective, single centre study, approved by the National Research Ethics Committee, enrolling patients presenting for emergency PPCI after obtaining informed consent. We included adults (≥18 years) with a presumed diagnosis of STEMI based on clinical presentation and ECG criteria (namely: new ST-elevation at the J-point in ≥2 contiguous leads of ≥2mm [0.2mV] in men or ≥1.5mm [0.15mV] in women in leads V2–V3 and/or of ≥1mm [0.1mV] in other contiguous chest leads or limb leads, or ST-depression in ≥2 precordial leads [V1–V4], or new or presumably new left bundle branch block in patients with clinical suspicion of ongoing myocardial ischaemia) (10). All patients received aspirin 300mg and either clopidogrel 600mg or ticagrelor 180mg in the ambulance or emergency department upon diagnosis, before arrival at the heart attack centre (HAC). Patients receiving clopidogrel (rather than ticagrelor) pre-arrival to the cardiac catheterisation laboratory were loaded with ticagrelor 180mg orally peri-PPCI (after the first blood sample was taken) and continued on this post-procedure. Chest pain described by the patient as severe was treated by the emergency team with intravenous morphine (5-10mg), together with ondansetron for the prevention of nausea and vomiting, *en route* to the HAC. Patients who were vomiting following DAPT loading pre-PPCI, those intubated and ventilated, unable to swallow, those receiving oral anticoagulation, those with known coagulation disorders or platelet count $<100x10^9$/L, haemoglobin <80g/L, known active malignancy, or inability to take DAPT, were excluded.

## Blood sampling for thrombotic status

Blood was taken at 2 time points: 1) baseline upon arrival to the catheterisation laboratory (after DAPT loading, day 0), prior to heparin or glycoprotein IIb/IIIa inhibitor (GPI)

administration and before PPCI, and 2) on day 2 of admission (on DAPT), 2-4 hours after the morning dose of DAPT. Fasting was not required.

The first blood samples were taken from a 6-F radial or femoral sheath using a 2-syringe technique. The second samples were taken from an antecubital vein using an 18-G butterfly cannula also using a 2-syringe technique, taking care to avoid prolonged tourniquet time. The 2-syringe technique involved using the first 5ml blood for routine blood tests and the second 5ml for thrombotic status assessment. Prior data had shown no difference in thrombotic status between simultaneously collected arterial and venous blood samples.

## Assessment of global thrombotic status

The Global Thrombosis Test (GTT) (Thromboquest Ltd., London, UK), an automated point-of-care test, was used to assess both platelet reactivity and endogenous fibrinolysis from a native, non-anticoagulated blood sample. Measurement of thrombotic status was performed blinded to opiate use. The instrument was positioned in the catheterisation laboratory, ready to use. After the blood sample was obtained, it was introduced into the GTT cartridge within 15 seconds of withdrawal and the automated measurement begun. The instrument assesses the time taken to form an occlusive thrombus under high shear stress (occlusion time, OT), and the time required to restore flow through endogenous fibrinolysis (lysis time, LT). The principle of the GTT has previously been described in detail (11). In brief, blood flows under high shear through narrow gaps inside the conical tube where thrombus formation occurs and the instrument measures the time (d) between 2 consecutive blood drops downstream of this. This time interval increases gradually as flow slows and at an arbitrary point ($d \geq 15s$, before reaching complete occlusion), the end point of the measurement is displayed (occlusion time [OT], seconds). Restart of blood flow after occlusion is due to spontaneous fibrinolysis (lysis time [LT], seconds). If lysis does not occur until >6,000s (LT cut-off time), “no lysis” is

recorded. The coefficient of variation (cv) was assessed by testing 10 stable patients on 2 occasions, 48 hours apart**.**

## PPCI procedure

The procedure was performed according to standard clinical care. Unfractionated heparin (UFH) was given at a dose of 70-100 U/kg immediately before PPCI, with additional boluses to maintain the activated clotting time >250 seconds. Use of GPI was at the operator's discretion, in conjunction with UFH. Decisions regarding access site, thrombus aspiration, and stent type were left to the operator.

## ECG and Angiographic Analyses

ECG and angiographic analyses were performed by an investigator blinded to morphine use, thrombotic status results and not involved in the PPCI procedure. Standard 12-lead ECGs were obtained on arrival in the HAC and compared to that at baseline (in ambulance or emergency department). ECGs were analyzed using a hand-held caliper. The ST-segment was measured 20ms after the J-point, and the sum of ST deviation was measured as previously described (12). The percent resolution of ST deviation from baseline to arrival was calculated, and categorized using Schröder's 3-component definition: complete (≥70%), partial (30-70%) and no (≤30%) ST-segment resolution. Flow in the infarct-related artery was reported using the Thrombolysis in Myocardial Infarction (TIMI) flow grading system and patency defined as TIMI grade 2 or 3 flow.

## Data collection and follow-up

Patient case-notes were checked throughout the course of the index admission, to allow contemporaneous data collection. Patients were followed up at 30 days in person for the

occurrence of death, new MI (based on the universal definition of myocardial infarction according to European Society of Cardiology [ESC] guidelines) (13) including acute stent thrombosis (defined according to the Academic Research Consortium criteria), or stroke, as well as for major and minor bleeding, classified according to the Bleeding Academic Research Consortium (BARC) definition (14). For all endpoints, source documents were obtained and diagnosis verified by 2 clinicians blinded to medication or GTT results.

## Statistical analysis

Since there is no reference study examining the effect of morphine on troponin level in STEMI patients, we performed an internal pilot study of 51 patients to estimate final sample size. The troponin levels of patients who had (n=38) and had not received morphine (n=13) were 3922±1225 and 3472±987 ng/L, respectively. Based on this and assuming a two-sided alpha value of 0.05 and 3:1 ratio, we calculated using the t-test for independent variables, that enrolment of 284 patients would provide 80% power to demonstrate a significant difference in troponin values between patients who did and did not receive morphine. We recruited 300 patients to achieve suitable numbers for analysis.

Data are presented as mean and standard deviation (when normally distributed) or median and inter-quartile range (IQR, if non-normally distributed). Dichotomous variables were compared using chi-square test or Fisher's exact test, as appropriate. Correlations were analysed using Pearson's or Spearman's method, dependent on distribution. Patients were divided into two groups according to morphine use and subsequently also according to GPI use. Effects of clinical and angiographic variables, medications, and ECG parameters on thrombotic status were assessed.

Univariate and multivariate linear regression models were used to identify the independent predictors of peak troponin and binary logistic regression for ST-segment resolution failure. All the study variables listed in Tables 1, 2 and 3, were first analysed with univariate analysis

and those that showed a significant interaction ($p<0.05$) were entered into the multivariate analysis. Significance was taken as <0.05. Analyses were performed with Stata V.11.2 (StataCorp, College Station, Texas, USA).

# Results

Between April 2015 and June 2016, 337 patients presenting for emergency PPCI were eligible for recruitment. Four patients were already enrolled in the trial and 33 met ≥1 exclusion criteria. All survivors were followed up at 30 days. Intravenous morphine was given pre-hospital in 218 (72.7%) patients with intravenous ondansetron 4mg, given simultaneously. Patient characteristics are shown in Tables 1-3. Patients in the morphine and no-morphine groups were well matched for baseline characteristics.

Among patients who had received morphine, complete ST-segment resolution pre-PPCI was far less frequently observed (9.2 vs. 31.7%, $p<0.001$) and angiographic flow in the infarct-related artery was significantly reduced prior to PCI (21.6 vs. 48.8%, $p=0.001$) compared to those who had not received morphine (Figure 1 and Table 3).

Morphine-treated patients exhibited enhanced platelet reactivity on arrival, as evidenced by shorter OT, and impaired endogenous fibrinolysis (longer LT) compared to patients without morphine (Table 2). The difference in OT was no longer apparent by day 2, although LT remained slightly longer in the morphine-treated group (Table 2).

Patients receiving morphine had significantly higher peak troponin than those not receiving morphine (1906[1002-4398] vs. 1268[249-2920]; $p=0.016$), with a positive correlation between morphine use and troponin level ($r=0.2$, $p=0.012$).

Subgroup analysis showed that within the group of patients who received GPI (n=101), there was no difference in pre-PPCI coronary flow or peak troponin according to morphine use (Table 4).

Of all variables in Tables 1-3, univariate analysis showed that only the following were related to peak troponin level and were subsequently entered into the multiple linear regression analysis: ST-segment resolution failure ($p=0.001$), TIMI 0/1 angiographic flow pre-PPCI ($p<0.001$), impaired left ventricular function ($p<0.001$), anterior STEMI ($p=0.019$), baseline neutrophil count ($p=0.002$), and prior calcium antagonist use ($p=0.043$). Morphine use did

not predict peak troponin. Using multivariate linear regression, only anterior STEMI (p=0.020) and high neutrophil count (p=0.001) were independent predictors of troponin levels after adjustment for the other variables.

Of all variables in Tables 1-3, the following variables identified on univariate analysis were related to ST-segment resolution: morphine use (OR 0.21; CI:0.11-0.39; p<0.001), troponin T level (OR 0.95; CI:0.93-0.98; p<0.001), anterior STEMI (OR 0.53; CI:0.27-0.97; p=0.047), and pain to first device time (OR 0.34; CI:0.11-0.99; p=0.049). These variables were entered into the multivariate logistic regression analysis to identify independent predictors of ST-segment resolution. Only peak troponin (OR 0.93; CI:0.91-0.95; p<0.001) and morphine use (OR 0.26; CI:0.08-0.84; p=0.025) remained independent predictors of ST-segment resolution after adjustment for other variables.

There was no significant difference in the event rates between the groups (Tables 5 and 6). However, numerically more MACE events were observed in the morphine group.

The cv was 8% for OT and 10% for LT. There was a negative correlation between baseline OT and neutrophil count (r= -0.2, p=0.004), platelet count (r= -0.2, p=0.016) and baseline LT (r= -0.3, p<0.001). There was a positive correlation between baseline OT and fibrinogen (r= 0.2, p=0.007) and day 2 OT (r= 0.4, p<0.001). No other clinical, laboratory or angiographic parameters correlated with baseline OT or LT. There was no difference in the time of day at presentation between morphine and no-morphine groups (p=0.734), and no relationship between time of presentation and baseline OT (p=0.298) or LT (p=0.542).

# Discussion

In the largest study to date assessing the effect of morphine in STEMI, our non-randomized

data show that morphine administration is associated with impaired thrombotic status at presentation (evidenced by enhanced platelet reactivity and impaired endogenous fibrinolysis), reduced rate of spontaneous ST-segment resolution, reduced epicardial coronary flow pre-PPCI and higher peak troponin. Additional treatment with GPI appears to favourably influence these effects of morphine.

Spontaneous reperfusion, reported in 15% of patients with STEMI (15) is associated with a lower adverse event rate compared with persistent ST-segment elevation (16). Whilst a previous study showed no impact of morphine on reperfusion assessed 30 minutes *following* PPCI (3), we show that morphine use is associated with a significantly lower rate of *spontaneous* reperfusion (pre-PPCI) and is an independent predictor of failure of ST-segment resolution after adjusting for other variables. Furthermore, despite successful revascularization with similar post-PPCI coronary flow, peak troponin was significantly higher in the morphine group. Peak troponin levels following STEMI correlate closely with infarct size on cardiac MRI (17) and SPECT (18). The higher troponin level seen here in morphine-treated patients do not prove a causative association, but are supported by the larger infarct and lower myocardial salvage index on cardiac MRI following PPCI in morphine-treated patients (19). However, the larger infarct size did not translate into an increase in short-term adverse events, perhaps due to small sample size, coupled with relatively high use of GPI in our study, that may overcome the adverse effects of morphine.

The association of morphine with reduced flow, impaired thrombotic status and greater troponin rise may simply reflect the fact that patients with more extensive infarcts have more pain and analgesia requirement. Conversely, patients with efficient endogenous fibrinolysis may more frequently exhibit spontaneous reperfusion, thus have lower analgesia requirements and less troponin rise. However, in clinical practice, the extent of infarction is not always mirrored by the level of morphine requirement or administration. Variation in pain threshold between individuals, as well as degree of supporting collaterals, may affect the

intensity of pain experienced; furthermore, medical staff including paramedics have varying thresholds for administering analgesia. A randomized trial could address this confounder, but might face ethical challenges.

The apparent adverse effect of morphine is likely to be attributable, at least in part, to reduced gastric motility and delayed absorption of antiplatelet medication, and not a simple association of need for morphine with extensive infarction. This is supported by data from the IMPRESSION trial, which demonstrated reduction in the pharmacokinetic, pharmacodynamic and anti-platelet effects of ticagrelor when combined with morphine, compared to placebo (4).

Our study confirms and significantly enhances the findings of two earlier, small studies, of 70 (35 morphine-treated) (4) and 182 (74 morphine-treated) patients (3) showing that morphine attenuated $P2Y_{12}$ inhibitor effect in PPCI patients. Our trial is not only significantly larger, with 218 morphine-treated patients, but we show both an impact on platelet reactivity and an adverse relationship between morphine administration and spontaneous reperfusion pre-PPCI and infarct size post-PPCI.

High platelet reactivity is a marker of adverse outcome in the settings of ACS and PCI (20). The association of morphine use with enhanced platelet reactivity upon arrival, is likely attributable to delayed DAPT absorption. The mechanism linking $P2Y_{12}$ inhibition with enhanced reperfusion pre-PPCI is not clear. Data suggest that $P2Y_{12}$ inhibitors and GPI not only prevent formation of a stable arterial thrombus, but also loosen the formed thrombus, causing it to disperse. Platelet thrombi formed by perfusing blood over collagen were completely dispersed by the $P2Y_{12}$ inhibitor cangrelor or a GPI (21), and $P2Y_{12}$ inhibitors including clopidogrel, have been shown to destabilize platelet-platelet contacts, leading to thrombus disaggregation (22, 23). We postulate that morphine, by delaying DAPT absorption, attenuated $P2Y_{12}$ inhibitor effect, leading to delay in destabilizing platelet-platelet contacts, resulting in prolonged endogenous fibrinolysis. Although tirofiban was given only

in the catheterisation laboratory, the rapid onset of action may explain the improved flow pre-PPCI and reduced peak troponin. This is conjecture only and future prospective, randomised trials would be required to confirm this.

Endogenous fibrinolysis is a natural protective mechanism against lasting infarction (24), and impaired fibrinolysis is a marker of adverse prognosis in ACS (11) and STEMI (25). We observed a significant association between morphine administration and impaired endogenous fibrinolysis on arrival. The lower fibrinogen levels in patients receiving morphine, coupled with impaired endogenous fibrinolysis, may indicate systemic activation of the clotting system with consumption of clotting factors exceeding synthesis.

There is mounting evidence that opiate-use in the setting of STEMI may be harmful (3, 4, 26). Although in healthy volunteers, morphine significantly decreased the plasma concentrations of prasugrel (27) and ticagrelor (28) and their active metabolites, interestingly, morphine did not diminish the pharmacodynamic effects of these $P2Y_{12}$ inhibitors on platelet aggregation. However, this is a very different scenario to patients with coronary disease and those with acute coronary disease. Kubica and co-workers elegantly reviewed the possible mechanisms of the drug-drug interaction between morphine and $P2Y_{12}$ inhibitors, showing delay in pharmacokinetics, mirrored by delay in pharmacodynamic effects on platelet reactivity (29). This appears to be a class effect, with fentanyl administration also recently shown to also lower plasma concentrations of ticagrelor and delay its antiplatelet effects in the PACIFY trial (30). Options to overcome this include the use of non-opiate analgesia pre-hospital (such as intravenous paracetamol), or parenteral administration of $P2Y_{12}$ inhibitor, such as cangrelor, although cost is likely to be a deterrent for routine use (26, 29). Crushed ticagrelor is absorbed more quickly than oral tablets (9) and faster via a crushed oral compared to crushed sublingual route (31). Upfront GPI use may alleviate the adverse effect of morphine, since amongst patients receiving GPI, there was no difference in epicardial coronary flow pre-PPCI, nor in peak troponin, according to morphine use. Our data are

supported by an earlier small study in STEMI patients, showing that the delayed onset of platelet inhibition by prasugrel due to co-administration of morphine was overcome by intravenous abciximab (32) and in clopidogrel nonresponders, GPI use lowered the rate of cardiovascular events after elective PCI (33). Tirofiban is a small, nonpeptide molecule, with a short half-life and marked specificity for the GPIIb/IIIa receptor. Abciximab, a large monoclonal antibody directed against $\beta_3$ integrin, has a prolonged half-life, and also binds to $\alpha_v\beta_3$ integrin and to white-cell $\alpha_M\beta_2$ integrin receptors. Both agents are highly effective at blocking platelet-platelet interactions, but since abciximab can also inhibit platelet adhesion to endothelial cells and to white cells, there has been debate whether it may be superior to tirofiban (34, 35). Although tirofiban offered less protection from ischaemic events than abciximab in the TARGET trial (36), STEMI patients were excluded. A subsequent meta-analysis concluded that in PPCI patients, GPI provided a "class effect" benefit that extended also to small molecules such as tirofiban (34). But perhaps it is not the agent, but the timing of administration that matters most. Very early abciximab use pre-PPCI achieved an 89% reduction in the six-month end-point and enhanced TIMI 3 flow pre-PPCI >3-fold (35). Tirofiban administration ~33 minutes pre-PPCI significantly improved initial epicardial flow and myocardial perfusion compared to administration in the catheterisation laboratory (37). Whilst our current use of GPI is predominantly for high thrombus burden or bail-out during PPCI, consistent with the class IIa recommendation from guidelines (1, 38), in the present study tirofiban was administered at the operator's discretion at a variable timepoint, from presentation to just before PCI. Although it is not possible to derive the exact time between GPI administration and first culprit vessel image (due to documentation), we speculate that this would average 5-10 minutes. This is a shorter timeframe than that previously evaluated but benefits are consistent with the known rapid onset of effect. Whilst the observed relationship between GPI use and pre-PPCI coronary flow may be due to chance, the relationship with reduced troponin post-PPCI is consistent with earlier studies. Whilst routine

use in the PPCI setting remains contentious, there may be a selective role for GPI in patients who receive opiate analgesia, where DAPT absorption may be delayed.

Anti-emetics are frequently co-administered with opiates. Metoclopramide stimulates upper gastrointestinal tract motility, which may antagonise the adverse effects of opioid analgesia on the gut (29). Ondansetron, unlike metoclopramide, is not a pro-kinetic agent but whether it adversely impacts on upper gastrointestinal motility is contentious. It may slow whole gut transit, cause constipation, and reduce fasting antroduodenal motility (39). Whether metoclopramide may offer an advantage over ondansetron with regard to DAPT absorption, requires investigation.

## Study limitations

The main limitation of our study is that this was not a randomized controlled trial. A potential confounder resulting from the observational nature of this study, is that patients without spontaneous reperfusion may have more pain and greater analgesia requirement. Enhanced sympathetic activation in those with more pain might also influence thrombotic status through direct and indirect cholinergic effects on platelet aggregation. It would be unethical to withhold potent analgesia from STEMI patients and currently there are no suitable alternatives in the pre-hospital setting for routine use. However, the groups were well matched for baseline clinical, angiographic and haematological/biochemical profiles. Secondly, the majority of patients received clopidogrel pre-PPCI, whilst the ESC recommends prasugrel or ticagrelor in this setting, because of their faster onset of action, greater potency and superiority over clopidogrel in large outcome trials (1). However, in most of the United Kingdom, clopidogrel remains the standard $P2Y_{12}$ inhibitor administered in the ambulance, due to cost and complex funding arrangements, and this is also the case in many other European countries. Whilst the use of clopidogrel clearly impacts on the translatability of our results to a population receiving these more potent agents, the applicability of our data

is supported by similar adverse effects seen with morphine when patients received ticagrelor or prasugrel for PPCI (3). Furthermore, although most patients received clopidogrel, they were loaded with ticagrelor peri-PPCI and earlier data from the ATLANTIC (Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery) study has shown that pre-PPCI coronary reperfusion was similar whether ticagrelor loading was given pre-hospital or in the catheterisation laboratory (31). There were statistically more stents per patient implanted in the morphine than in the no-morphine group, although this difference was small, and stent diameter was similar between groups. We think this is unlikely to have impacted on 30 day outcomes, particularly as stent length, if anything, would more likely predispose to stent thrombosis, but this was not observed at follow up.

### Conclusions

In the largest study to-date examining the effects of morphine in STEMI, our non-randomized data show that morphine use is associated with enhanced platelet reactivity and impaired endogenous fibrinolysis, reduced occurrence of spontaneous reperfusion pre-PPCI and non-independently associated with larger infarct size, and that these adverse effects of morphine may be influenced by GPI administration.

## Funding

This work was supported by the Research & Development Department, East and North Hertfordshire NHS Trust.

## Conflicts of interest

There are no conflicts of interest pertaining to this manuscript. For transparency, DAG is related through family to a company director in Thromboquest Ltd., which manufactures the Global Thrombosis Test, but neither she, nor her spouse or children have financial involvement or equity interest in this company, and the company has had no involvement in the design, conduct or finance of this study. The other authors have reported no relationships relevant to the contents of this paper to disclose.

# References


1. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, 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. 2017.

2. Hobl EL, Stimpfl T, Ebner J, Schoergenhofer C, Derhaschnig U, Sunder-Plassmann R, et al. Morphine decreases clopidogrel concentrations and effects: a randomized, double-blind, placebo-controlled trial. J Am Coll Cardiol. 2014;63(7):630-5.

3. Bellandi B, Zocchi C, Xanthopoulou I, Scudiero F, Valenti R, Migliorini A, et al. Morphine use and myocardial reperfusion in patients with acute myocardial infarction treated with primary PCI. Int J Cardiol. 2016;221:567-71.

4. Kubica J, Adamski P, Ostrowska M, Sikora J, Kubica JM, Sroka WD, 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(3):245-52.

5. Parodi G, Valenti R, Bellandi B, Migliorini A, Marcucci R, Comito V, et al. Comparison of prasugrel and ticagrelor loading doses in ST-segment elevation myocardial infarction patients: RAPID (Rapid Activity of Platelet Inhibitor Drugs) primary PCI study. J Am Coll Cardiol. 2013;61(15):1601-6.

6. Thomas MR, Morton AC, Hossain R, Chen B, Luo L, Shahari NN, et al. Morphine delays the onset of action of prasugrel in patients with prior history of ST-elevation myocardial infarction. Thromb Haemost. 2016;116(1):96-102.

7. Silvain J, Storey RF, Cayla G, Esteve JB, Dillinger JG, Rousseau H, et al. P2Y12 receptor inhibition and effect of morphine in patients undergoing primary PCI for ST-segment elevation myocardial infarction. The PRIVATE-ATLANTIC study. Thromb Haemost. 2016;116(2):369-78.

8. Parodi G, Bellandi B, Xanthopoulou I, Capranzano P, Capodanno D, Valenti R, 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. 2015;8(1).

9. Parodi G, Xanthopoulou I, Bellandi B, Gkizas V, Valenti R, Karanikas S, et al. Ticagrelor crushed tablets administration in STEMI patients: the MOJITO study. J Am Coll Cardiol. 2015;65(5):511-2.

10. Steg PG, James SK, Atar D, Badano LP, Blömstrom-Lundqvist C, Borger MA, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2012;33(20):2569-619.

11. Saraf S, Christopoulos C, Salha IB, Stott DJ, Gorog DA. Impaired endogenous thrombolysis in acute coronary syndrome patients predicts cardiovascular death and nonfatal myocardial infarction. J Am Coll Cardiol. 2010;55(19):2107-15.

12. de Lemos JA, Antman EM, Giugliano RP, McCabe CH, Murphy SA, Van de Werf F, et al. ST-segment resolution and infarct-related artery patency and flow after thrombolytic therapy. Thrombolysis in Myocardial Infarction (TIMI) 14 investigators. Am J Cardiol. 2000;85(3):299-304.

13. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. Eur Heart J. 2012;33(20):2551-67.

14. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation. 2011;123(23):2736-47.

15. Bainey KR, Fu Y, Wagner GS, Goodman SG, Ross A, Granger CB, et al. Spontaneous reperfusion in ST-elevation myocardial infarction: comparison of angiographic and electrocardiographic assessments. Am Heart J. 2008;156(2):248-55.

16. Fefer P, Hod H, Hammerman H, Boyko V, Behar S, Matetzky S, et al. Relation of clinically defined spontaneous reperfusion to outcome in ST-elevation myocardial infarction. Am J Cardiol. 2009;103(2):149-53.

17. Giannitsis E, Steen H, Kurz K, Ivandic B, Simon AC, Futterer S, et al. Cardiac magnetic resonance imaging study for quantification of infarct size comparing directly serial versus single time-point measurements of cardiac troponin T. J Am Coll Cardiol. 2008;51(3):307-14.

18. Arruda-Olson AM, Roger VL, Jaffe AS, Hodge DO, Gibbons RJ, Miller TD. Troponin T levels and infarct size by SPECT myocardial perfusion imaging. JACC Cardiovasc Imaging. 2011;4(5):523-33.

19. de Waha S, Eitel I, Desch S, Fuernau G, Lurz P, Urban D, et al. Intravenous morphine administration and reperfusion success in ST-elevation myocardial infarction: insights from cardiac magnetic resonance imaging. Clin Res Cardiol. 2015;104(9):727-34.

20. Gurbel PA, Jeong YH, Navarese EP, Tantry US. Platelet-Mediated Thrombosis: From Bench to Bedside. Circ Res. 2016;118(9):1380-91.

21. Goto S, Tamura N, Ishida H, Ruggeri ZM. Dependence of platelet thrombus stability on sustained glycoprotein IIb/IIIa activation through adenosine 5'-diphosphate receptor stimulation and cyclic calcium signaling. J Am Coll Cardiol. 2006;47(1):155-62.

22. Cosemans JM, Munnix IC, Wetzker R, Heller R, Jackson SP, Heemskerk JW. Continuous signaling via PI3K isoforms beta and gamma is required for platelet ADP receptor function in dynamic thrombus stabilization. Blood. 2006;108(9):3045-52.

23. Hosokawa K, Ohnishi T, Fukasawa M, Kondo T, Sameshima H, Koide T, et al. A microchip flow-chamber system for quantitative assessment of the platelet thrombus formation process. Microvasc Res. 2012;83(2):154-61.

24. Okafor O, Gorog D. Endogenous fibrinolysis: an important mediator of thrombus formation and cardiovascular risk. J Am Coll Cardiol. 2015;65:1683-99.

25. Christopoulos C, Farag M, Sullivan K, Wellsted D, Gorog DA. Impaired thrombolytic status predicts adverse cardiac events in patients undergoing primary percutaneous coronary intervention. Thromb Haemost. 2015.

26. Giannopoulos G, Deftereos S, Kolokathis F, Xanthopoulou I, Lekakis J, Alexopoulos D. P2Y12 Receptor Antagonists and Morphine: A Dangerous Liaison? Circ Cardiovasc Interv. 2016;9(9).

27. Hobl EL, Reiter B, Schoergenhofer C, Schwameis M, Derhaschnig U, Lang IM, et al. Morphine interaction with prasugrel: a double-blind, cross-over trial in healthy volunteers. Clin Res Cardiol. 2016;105(4):349-55.

28. Hobl EL, Reiter B, Schoergenhofer C, Schwameis M, Derhaschnig U, Kubica J, et al. Morphine decreases ticagrelor concentrations but not its antiplatelet effects: a randomized trial in healthy volunteers. Eur J Clin Invest. 2016;46(1):7-14.

29. Kubica J, Kubica A, Jilma B, Adamski P, Hobl EL, Navarese EP, et al. Impact of morphine on antiplatelet effects of oral P2Y12 receptor inhibitors. Int J Cardiol. 2016;215:201-8.

30. McEvoy JW, Ibrahim K, Kickler TS, Clarke WA, Hasan RK, Czarny MJ, et al. Effect of Intravenous Fentanyl on Ticagrelor Absorption and Platelet Inhibition Among Patients Undergoing Percutaneous Coronary Intervention: The PACIFY Randomized Clinical Trial. Circulation. 2017.

31. Niezgoda P, Sikora J, Barańska M, Sikora A, Buszko K, Siemińska E, et al. Crushed sublingual versus oral ticagrelor administration strategies in patients with unstable angina. A pharmacokinetic/pharmacodynamic study. Thromb Haemost. 2017;117(4):718-26.

32. Siller-Matula JM, Specht S, Kubica J, Alexopoulos D, De Caterina R, Hobl EL, et al. Abciximab as a bridging strategy to overcome morphine-prasugrel interaction in STEMI patients. Br J Clin Pharmacol. 2016;82(5):1343-50.

33. Cuisset T, Frere C, Quilici J, Morange PE, Mouret JP, Bali L, et al. Glycoprotein IIb/IIIa inhibitors improve outcome after coronary stenting in clopidogrel nonresponders: a prospective, randomized study. JACC Cardiovasc Interv. 2008;1(6):649-53.

34. De Luca G, Ucci G, Cassetti E, Marino P. Benefits from small molecule administration as compared with abciximab among patients with ST-segment elevation myocardial infarction treated with primary angioplasty: a meta-analysis. J Am Coll Cardiol. 2009;53(18):1668-73.

35. Topol EJ, Neumann FJ, Montalescot G. A preferred reperfusion strategy for acute myocardial infarction. J Am Coll Cardiol. 2003;42(11):1886-9.

36. Topol EJ, Moliterno DJ, Herrmann HC, Powers ER, Grines CL, Cohen DJ, et al. Comparison of two platelet glycoprotein IIb/IIIa inhibitors, tirofiban and abciximab, for the prevention of ischemic events with percutaneous coronary revascularization. N Engl J Med. 2001;344(25):1888-94.

37. Lee DP, Herity NA, Hiatt BL, Fearon WF, Rezaee M, Carter AJ, et al. Adjunctive platelet glycoprotein IIb/IIIa receptor inhibition with tirofiban before primary angioplasty improves angiographic outcomes: results of the TIrofiban Given in the Emergency Room before Primary Angioplasty (TIGER-PA) pilot trial. Circulation. 2003;107(11):1497-501.

38. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery

(EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J. 2014;35(37):2541-619.

39. Marciani L, Wright J, Foley S, Hoad CL, Totman JJ, Bush D, et al. Effects of a 5-HT(3) antagonist, ondansetron, on fasting and postprandial small bowel water content assessed by magnetic resonance imaging. Aliment Pharmacol Ther. 2010;32(5):655-63.

**Figure 1**

**Spontaneous reperfusion pre-PPCI, peak troponin and in-hospital adverse events in 300 patients with STEMI, according morphine use.**

TIMI=Thrombolysis in Myocardial Infarction, MACE=major adverse cardiovascular events (see text). *=P<0.02

## Table 1: Baseline Patient Characteristics

| | Whole Group (n=300) | Morphine (n=218) | No Morphine (n=82) | P Value |
|---|---|---|---|---|
| **Age, yrs** | 64±13 | 64±13 | 63±12 | 0.457 |
| **Male** | 236(78.7) | 170(78.0) | 66(80.5) | 0.923 |
| **Cardiogenic shock** | 18(6.0) | 15(6.9) | 3(3.7) | 0.418 |
| **Diabetes mellitus** | 52(17.3) | 34(15.6) | 18(22.0) | 0.318 |
| **Active smoker** | 99(33.0) | 75(34.4) | 24(29.3) | 0.601 |
| **Hypertension** | 151(50.3) | 107(49.1) | 44(53.7) | 0.739 |
| **Prior CAD** | 43(14.3) | 31(14.2) | 12(14.6) | 1.000 |
| **Prior MI** | 34(11.3) | 24(11.0) | 10(12.2) | 0.840 |
| **Prior PCI** | 33(11.0) | 25(11.5) | 8(9.8) | 0.837 |
| **Prior CABG** | 4(1.3) | 3(1.4) | 1(1.2) | 1.000 |
| **Renal insufficiency** | 12(4.0) | 6(2.8) | 6(7.3) | 0.104 |
| **PVD** | 13(4.3) | 8(3.7) | 5(6.1) | 0.527 |
| **Prior CVA** | 11(3.7) | 9(4.1) | 2(2.4) | 0.733 |
| **Prior aspirin use** | 50(16.7) | 36(16.5) | 14(17.1) | 1.000 |
| **Prior $P2Y_{12}$ inhibitor use** | 11(3.7) | 9(4.1) | 3(3.7) | 1.000 |
| **$P2Y_{12}$ inhibitor loading agent** | | | | |
| **Clopidogrel** | 259(86.3) | 189(86.7) | 70(85.4) | 1.000 |
| **Ticagrelor** | 41(13.7) | 29(13.3) | 12(14.6) | 0.853 |
| **Time from $P2Y_{12}$ inhibitor loading to first blood sample (min) *** | 46[38-59] | 47[36-60] | 46[39-58] | 0.740 |
| **Medications on Day 2** | | | | |
| **Aspirin** | 291(97.0) | 212(97.2) | 79(96.3) | 1.000 |
| **Ticagrelor** | 237(79.0) | 174(79.8) | 63(76.8) | 0.922 |
| **Clopidogrel** | 52(17.3) | 38(17.4) | 14(17.1) | 1.000 |
| **Prasugrel** | 2(0.7) | 1(0.5) | 1(1.2) | 0.475 |
| **Beta-blocker** | 266(88.7) | 194(89.0) | 72(87.8) | 1.000 |
| **ACE inhibitor** | 269(89.7) | 198(90.8) | 71(86.6) | 0.850 |
| **Calcium antagonist** | 23(7.8) | 13(6.0) | 10(12.2) | 0.147 |
| **Statin** | 283(94.3) | 206(94.5) | 77(93.9) | 1.000 |
| **Nitrate** | 14(4.7) | 10(4.6) | 4(4.9) | 1.000 |
| **Insulin** | 15(5.0) | 9(4.1) | 6(7.3) | 0.375 |

Values are mean±SD or n(%), except * where values median[IQR]. Renal insufficiency was defined as creatinine levels >177 μmol/L. Prior aspirin or $P2Y_{12}$ inhibitor use defined as regular $P2Y_{12}$ inhibitor use before hospitalisation.

ACE: angiotensin-converting enzyme, CABG: coronary artery bypass grafting, CAD: coronary artery disease, CVA: cerebrovascular accident, MI: myocardial infarction, PCI: percutaneous coronary intervention, PVD: peripheral vascular disease.

**Table 2: Haematological and biochemical profiles**

| | Whole Group (n=300) | Morphine (n=218) | No Morphine (n=82) | P Value |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| **Haemoglobin (g/L) *** | 139±16 | 139±16 | 138±17 | 0.899 |
| **Haematocrit (%) *** | 42±5 | 42±5 | 42±5 | 0.897 |
| **Neutrophil count (x$10^9$/L)** | 7.3[5.7-9.4] | 7.4[5.8-9.6] | 7.0[5.5-8.6] | 0.264 |
| **Platelet count (x$10^9$/L)** | 238[197-277] | 242[199-285] | 229[196-268] | 0.209 |
| **Creatinine (µmol/L)** | 81[70-95] | 81[70-95] | 86[71-99] | 0.178 |
| **Peak troponin T (ng/L)** | 1798[736-3961] | 1906[1002-4398] | 1268[249-2920] | 0.016 |
| **Fibrinogen (g/L)** | 4.4[3.8-5.0] | 4.3[3.8-4.9] | 4.6[4.1-5.4] | 0.021 |
| **Total cholesterol (mmol/L)** | 5.2[4.2-5.9] | 5.2[4.2-5.9] | 5.2[4.5-5.9] | 0.521 |
| **Baseline OT (sec) *** | 400±179 | 347±150 | 547±182 | <0.001 |
| **Day 2 OT (sec) *** | 477±132 | 469±128 | 488±143 | 0.339 |
| **Baseline LT (sec)** | 1358[1107-1684] | 1402[1159-1809] | 1185[1029-1541] | 0.001 |
| **Day 2 LT (sec)** | 1321[1165-1582] | 1332[1184-1584] | 1220[1131-1478] | 0.034 |

Values are median[IQR], except * where values are mean±SD. LT: lysis time; OT: occlusion time. All values measured at presentation, except peak troponin and day 2 OT and LT.

Normal values: haemoglobin 130-180g/L (males) and 115-165g/L (females); haematocrit 40-52% (males) and 36-47% (females); neutrophil count 2-7.5x$10^9$/L; platelet count 150-400x$10^9$/L; creatinine 60-110µmol/L (males) and 45-90µmol/L (females); troponin T<14 ng/L (Elecsys high-sensitivity assay, Roche Diagnostics); fibrinogen 2–4 g/L; total cholesterol ≤4.0 mmol/L.

## Table 3: Angiographic, Interventional and Echocardiographic Patient Characteristics

| | **Whole Group (n=300)** | **Morphine (n=218)** | **No Morphine (n=82)** | **P Value** |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| **ST-segment resolution on ECG pre-PPCI** | 49(16.3) | 21(9.6) | 28(34.1) | <0.001 |
| **Complete (≥70%)** | 46(15.3) | 20(9.2) | 26(31.7) | <0.001 |
| **Partial (30% to 70%)** | 3(1.0) | 1(0.4) | 2(2.4) | 0.187 |
| **TIMI 2/3 angiographic flow pre-PPCI** | 87(29.0) | 47(21.6) | 40(48.8) | 0.001 |
| **TIMI 2/3 angiographic flow post-PPCI** | 292(97.3) | 213(97.7) | 79(96.3) | 1.000 |
| **Myocardial blush grade 2/3 post-PPCI *** | 281(93.7) | 203(93.1) | 78(95.1) | 0.926 |
| **Systolic blood pressure (mmHg) on arrival** | 136[119-158] | 135[117-154] | 140[120-168] | 0.052 |
| **Diastolic blood pressure (mmHg) on arrival** | 80[68-90] | 80[68-90] | 82[69-99] | 0.249 |
| **Heart rate (bpm) on arrival** | 77[66-90] | 75[65-90] | 80[70-89] | 0.188 |
| **Killip classification** | | | | |
| **Score≤2** | 275(91.7) | 200(91.7) | 75(91.5) | 1.000 |
| **Score>2** | 25(8.3) | 18(8.3) | 7(8.5) | 1.000 |
| **Arterial access** | | | | |
| **Radial** | 258(86.0) | 185(84.9) | 73(89.0) | 0.850 |
| **Femoral** | 42(14.0) | 33(15.1) | 9(11.0) | 0.462 |
| **1-vessel disease** | 124(41.3) | 94(43.1) | 30(36.6) | 0.546 |
| **2-vessel disease** | 94(31.3) | 64(29.4) | 30(36.6) | 0.432 |
| **3-vessel disease** | 80(26.7) | 59(27.1) | 21(25.6) | 0.888 |
| **Culprit vessel** | | | | |
| **LMS** | 6(2.0) | 5(2.3) | 1(1.2) | 0.686 |
| **LAD** | 107(35.7) | 86(39.4) | 21(25.6) | 0.122 |
| **LCA** | 52(17.3) | 32(14.7) | 20(24.4) | 0.135 |
| **RCA** | 116(38.7) | 89(40.8) | 27(32.9) | 0.456 |
| **Bypass graft** | 1(0.3) | 1(0.5) | 0 | 1.000 |
| **Thrombus aspiration** | 58(19.3) | 45(20.6) | 13(15.9) | 0.517 |
| **Balloon predilatation** | 243(81.0) | 181(83.0) | 62(75.6) | 0.696 |
| **GPI (Tirofiban) use** | 101(33.7) | 79(36.2) | 22(26.8) | 0.296 |
| **Bivalirudin use** | 6(2.0) | 5(2.3) | 1(1.2) | 0.686 |
| **Balloon angioplasty only** | 16(5.3) | 11(5.0) | 5(6.1) | 0.776 |
| **Stent implantation** | | | | |
| **DES** | 250(83.3) | 190(87.2) | 60(73.2) | 0.381 |
| **BMS** | 8(2.7) | 8(3.7) | 0 | 0.115 |
| **Number of stents **** | 1.25±0.87 | 1.33±0.87 | 1.04±0.85 | 0.009 |
| **Stent diameter <3 mm** | 87(29) | 66(30.3) | 21(25.6) | 0.477 |
| **Door to first device time, min** | 29[22-35] | 29[22-35] | 30[21-36] | 0.918 |
| **Call to first device time, min** | 99[81-121] | 97[79-121] | 103[82-121] | 0.420 |
| **Pain to first device time, min** | 162[112-235] | 160[112-236] | 185[118-225] | 0.755 |
| **Left ventricular function** | | | | |

| | | | | |
|---|---|---|---|---|
| **Normal (EF ≥55%)** | 117(39.0) | 77(35.3) | 40(48.8) | 0.188 |
| **Mildly impaired (EF 45–54%)** | 72(24.0) | 55(25.2) | 17(20.7) | 0.556 |
| **Moderately impaired (EF 36–44%)** | 73(24.3) | 56(25.7) | 17(20.7) | 0.556 |
| **Severely impaired (EF ≤35%)** | 38(12.7) | 27(12.4) | 11(13.4) | 0.848 |

Values are median[IQR] or n(%), except ** where values are mean±SD. Left ventricular function was assessed by echocardiography prior to hospital discharge.

BMS: bare metal stent, DES: drug eluting stent, EF: ejection fraction, GPI: glycoprotein IIb/IIIa inhibitor, LAD: left anterior descending coronary artery, LCA: left circumflex coronary artery, OM: obtuse marginal coronary artery, PPCI: primary percutaneous coronary intervention, RCA: right coronary artery, TIMI: Thrombolysis in Myocardial Infarction.

Door to first device time was the delay between the arrival of a patient at the hospital and the time of first intracoronary device use (defined as time of first balloon or stent inflation; or use of thrombectomy or angioplasty wire if these re-established flow). Call to device time was the delay between a patient's call for help and first device time. Pain to device time was the delay between the onset of symptoms and first device time.

* All 19 patients (6.3%) who had final myocardial blush grade 0/1 showed ST-segment resolution failure and TIMI 0/1 angiographic flow pre-PPCI, and 5 out of 19 had TIMI 0/1 angiographic flow post-PPCI.

**Table 4: Spontaneous reperfusion, thrombotic status and peak troponin, according to morphine and GPI use**

| | Whole Group (n=300) | GPI (n=101) | | | | No GPI (n=199) | | | | P Value GPI vs No GPI |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Whole GPI group | Morphine (n=79) (Group 1) | No Morphine (n=22) (Group 2) | P Value Group 1 vs Group 2 | Whole No GPI group | Morphine (n=139) (Group 3) | No morphine (n=60) (Group 4) | P Value Group 3 vs Group 4 | |
| **ST-segment resolution on ECG pre-PPCI** | 49(16.3) | 6(5.9) | 2(2.5) | 4(18.2) | 0.029 | 43(21.6) | 19(13.7) | 24(40.0) | 0.002 | 0.002 |
| **TIMI 2/3 angiographic flow pre-PPCI** | 87(29.0) | 9(8.9) | 5(6.3) | 4(18.2) | 0.211 | 78(39.2) | 42(30.2) | 36(60.0) | 0.017 | <0.001 |
| **TIMI 2/3 angiographic flow post-PPCI** | 292(97.3) | 98(97.0) | 77(97.5) | 21(95.5) | 1.000 | 194(97.5) | 136(97.8) | 58(96.7) | 1.000 | 1.000 |
| **Peak troponin T (ng/L)** | 1798[736-3961] | 2646[1242-4694] | 2508[1248-5417] | 2879[1235-3691] | 0.636 | 1448[548-3030] | 1732[798-3796] | 1030[151-2313] | 0.018 | 0.007 |
| **Baseline OT (sec) *** | 400±179 | 373±202 | 321±154 | 559±242 | <0.001 | 414±164 | 364±146 | 531±147 | <0.001 | 0.066 |
| **Day 2 OT (sec) *** | 477±132 | 464±135 | 455±131 | 492±148 | 0.286 | 483±131 | 477±123 | 498±148 | 0.327 | 0.254 |
| **Baseline LT (sec)** | 1358[1107-1684] | 1405[1107-1673] | 1434[1140-1697] | 1192[1025-1555] | 0.061 | 1330[1105-1711] | 1390[1169-1850] | 1205[1042-1537] | 0.003 | 0.919 |
| **Day 2 LT (sec)** | 1321[1165-1582] | 1314[1166-1540] | 1326[1192-1531] | 1268[1154-1607] | 0.665 | 1321[1158-1585] | 1354[1185-1600] | 1218[1136-1431] | 0.026 | 0.904 |

Values are median[IQR] or n(%), except * where values are mean±SD. GPI: glycoprotein IIb/IIIa inhibitor, PPCI: primary percutaneous coronary intervention, TIMI: Thrombolysis in Myocardial Infarction, LT: lysis time; OT: occlusion time. Troponin T<14 ng/L (Elecsys high-sensitivity assay, Roche Diagnostics).

**Table 5: In-Hospital Outcome**

| Outcome | Whole group (n=300) | Morphine (n=218) | No Morphine (n=82) | P Value |
|---|---|---|---|---|
| MACE (death, re-infarction, CVA) | 12 | 10 | 2 | 0.525 |
| Death | 6 | 4 | 2 | 1.000 |
| New myocardial infarction or re-infarction | 3 | 3 | 0 | 0.566 |
| Stent thrombosis | 2 | 2 | 0 | 1.000 |
| Cerebrovascular accident | 3 | 3 | 0 | 0.566 |
| Major bleeding (BARC type 3-5) | 0 | 0 | 0 | 1.000 |
| Minor bleeding (BARC type ≤2) | 2 | 0 | 2 | 0.077 |
| Pulmonary oedema | 6 | 4 | 2 | 1.000 |
| Length of hospitalisation (days) | 3[2-4] | 3[2-4] | 2.5[2-4] | 0.515 |

Values are n except length of hospitalisation (median[IQR]). MACE: major adverse cardiovascular events (cumulative of death, myocardial infarction and CVA), CVA: cerebrovascular accident, BARC: Bleeding Academic Research Consortium.

All deaths were cardiovascular, defined as death in the presence of ACS, significant cardiac arrhythmia, or refractory congestive heart failure, or death attributed to cardiovascular cause at post-mortem. New MI or re-infarction was defined according to the universal definition of myocardial infarction (13) as the detection of rise and/or fall of troponin T with at least one value >99th percentile of the upper reference limit and with at least one of the following: symptoms of ischaemia, new or presumably new significant ST-T changes or new LBBB, development of pathological Q waves in the ECG, imaging evidence of new loss of viable myocardium, or new regional wall motion abnormality, identification of an intracoronary thrombus by angiography, or stent thrombosis associated with myocardial ischaemia detected by coronary angiography. Stent thromboses were all acute, defined according to the Academic Research Consortium criteria. All CVA were ischaemic, defined as an acute focal infarction of the brain with one of the following: sudden onset of a new focal neurologic deficit, with clinical or imaging evidence of infarction lasting 24 hours or more and not attributable to a non-ischaemic cause, a new focal neurologic deficit lasting <24 hours and not attributable to a non-ischaemic cause but accompanied by neuroimaging evidence of new brain infarction.

**Table 6: 30-day Outcome**

| Outcome | Whole group (n=300) | Morphine (n=218) | No Morphine (n=82) | P Value |
|---|---|---|---|---|
| MACE (death, re-infarction, CVA) | 20 | 18 | 2 | 0.115 |
| Death | 10 | 8 | 2 | 0.734 |
| New myocardial infarction or re-infarction | 6 | 6 | 0 | 0.197 |
| Stent thrombosis | 3 | 3 | 0 | 0.566 |
| Cerebrovascular accident | 4 | 4 | 0 | 0.344 |
| Major bleeding (BARC type 3-5) | 2 | 1 | 1 | 0.999 |
| Minor bleeding (BARC type ≤2) | 5 | 2 | 3 | 0.134 |
| Pulmonary oedema | 12 | 9 | 3 | 1.000 |

Values represent number of events. For abbreviations, see Table 5.

**Figure 1**