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

Short title: Morphine impairs reperfusion pre-PPCI

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## 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<sub>12</sub> 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<sub>12</sub> 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 ( $\geq 18$  years) with a presumed diagnosis of STEMI based on clinical presentation and ECG criteria (namely: new ST-elevation at the J-point in  $\geq 2$  contiguous leads of  $\geq 2$ mm [0.2mV] in men or  $\geq 1.5$ mm [0.15mV] in women in leads V2–V3 and/or of  $\geq 1$ mm [0.1mV] in other contiguous chest leads or limb leads, or ST-depression in  $\geq 2$  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  $< 100 \times 10^9/L$ , 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 ( $\geq 70\%$ ), partial (30-70%) and no ( $\leq 30\%$ ) 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  $3922 \pm 1225$  and  $3472 \pm 987$  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  $\geq 1$  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<sub>12</sub> 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<sub>12</sub> inhibition with enhanced reperfusion pre-PPCI is not clear. Data suggest that P2Y<sub>12</sub> 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<sub>12</sub> inhibitor cangrelor or a GPI (21), and P2Y<sub>12</sub> 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<sub>12</sub> 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<sub>12</sub> 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<sub>12</sub> 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<sub>12</sub> 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<sub>12</sub> 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.

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## **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.

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## **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**

	<b>Whole Group (n=300)</b>	<b>Morphine (n=218)</b>	<b>No Morphine (n=82)</b>	<b>P Value</b>
<b>Age, yrs</b>	64±13	64±13	63±12	0.457
<b>Male</b>	236(78.7)	170(78.0)	66(80.5)	0.923
<b>Cardiogenic shock</b>	18(6.0)	15(6.9)	3(3.7)	0.418
<b>Diabetes mellitus</b>	52(17.3)	34(15.6)	18(22.0)	0.318
<b>Active smoker</b>	99(33.0)	75(34.4)	24(29.3)	0.601
<b>Hypertension</b>	151(50.3)	107(49.1)	44(53.7)	0.739
<b>Prior CAD</b>	43(14.3)	31(14.2)	12(14.6)	1.000
<b>Prior MI</b>	34(11.3)	24(11.0)	10(12.2)	0.840
<b>Prior PCI</b>	33(11.0)	25(11.5)	8(9.8)	0.837
<b>Prior CABG</b>	4(1.3)	3(1.4)	1(1.2)	1.000
<b>Renal insufficiency</b>	12(4.0)	6(2.8)	6(7.3)	0.104
<b>PVD</b>	13(4.3)	8(3.7)	5(6.1)	0.527
<b>Prior CVA</b>	11(3.7)	9(4.1)	2(2.4)	0.733
<b>Prior aspirin use</b>	50(16.7)	36(16.5)	14(17.1)	1.000
<b>Prior P2Y<sub>12</sub> inhibitor use</b>	11(3.7)	9(4.1)	3(3.7)	1.000
<b>P2Y<sub>12</sub> inhibitor loading agent</b>				
<b>Clopidogrel</b>	259(86.3)	189(86.7)	70(85.4)	1.000
<b>Ticagrelor</b>	41(13.7)	29(13.3)	12(14.6)	0.853
<b>Time from P2Y<sub>12</sub> inhibitor loading to first blood sample (min) *</b>	46[38-59]	47[36-60]	46[39-58]	0.740
<b>Medications on Day 2</b>				
<b>Aspirin</b>	291(97.0)	212(97.2)	79(96.3)	1.000
<b>Ticagrelor</b>	237(79.0)	174(79.8)	63(76.8)	0.922
<b>Clopidogrel</b>	52(17.3)	38(17.4)	14(17.1)	1.000
<b>Prasugrel</b>	2(0.7)	1(0.5)	1(1.2)	0.475
<b>Beta-blocker</b>	266(88.7)	194(89.0)	72(87.8)	1.000
<b>ACE inhibitor</b>	269(89.7)	198(90.8)	71(86.6)	0.850
<b>Calcium antagonist</b>	23(7.8)	13(6.0)	10(12.2)	0.147
<b>Statin</b>	283(94.3)	206(94.5)	77(93.9)	1.000
<b>Nitrate</b>	14(4.7)	10(4.6)	4(4.9)	1.000
<b>Insulin</b>	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<sub>12</sub> inhibitor use defined as regular P2Y<sub>12</sub> 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**

<b>Whole Group (n=300)</b>	<b>Morphine (n=218)</b>	<b>No Morphine (n=82)</b>	<b>P Value</b>
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<b>Haemoglobin (g/L) *</b>	139±16	139±16	138±17	0.899
<b>Haematocrit (%) *</b>	42±5	42±5	42±5	0.897
<b>Neutrophil count (x10<sup>9</sup>/L)</b>	7.3[5.7-9.4]	7.4[5.8-9.6]	7.0[5.5-8.6]	0.264
<b>Platelet count (x10<sup>9</sup>/L)</b>	238[197-277]	242[199-285]	229[196-268]	0.209
<b>Creatinine (µmol/L)</b>	81[70-95]	81[70-95]	86[71-99]	0.178
<b>Peak troponin T (ng/L)</b>	1798[736-3961]	1906[1002-4398]	1268[249-2920]	0.016
<b>Fibrinogen (g/L)</b>	4.4[3.8-5.0]	4.3[3.8-4.9]	4.6[4.1-5.4]	0.021
<b>Total cholesterol (mmol/L)</b>	5.2[4.2-5.9]	5.2[4.2-5.9]	5.2[4.5-5.9]	0.521
<b>Baseline OT (sec) *</b>	400±179	347±150	547±182	<0.001
<b>Day 2 OT (sec) *</b>	477±132	469±128	488±143	0.339
<b>Baseline LT (sec)</b>	1358[1107-1684]	1402[1159-1809]	1185[1029-1541]	0.001
<b>Day 2 LT (sec)</b>	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 2-7.5x10<sup>9</sup>/L; platelet count 150-400x10<sup>9</sup>/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**

	<b>Whole Group (n=300)</b>	<b>Morphine (n=218)</b>	<b>No Morphine (n=82)</b>	<b>P Value</b>
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<b>ST-segment resolution on ECG pre-PPCI</b>	49(16.3)	21(9.6)	28(34.1)	<0.001
<b>Complete (≥70%)</b>	46(15.3)	20(9.2)	26(31.7)	<0.001
<b>Partial (30% to 70%)</b>	3(1.0)	1(0.4)	2(2.4)	0.187
<b>TIMI 2/3 angiographic flow pre-PPCI</b>	87(29.0)	47(21.6)	40(48.8)	0.001
<b>TIMI 2/3 angiographic flow post-PPCI</b>	292(97.3)	213(97.7)	79(96.3)	1.000
<b>Myocardial blush grade 2/3 post-PPCI *</b>	281(93.7)	203(93.1)	78(95.1)	0.926
<b>Systolic blood pressure (mmHg) on arrival</b>	136[119-158]	135[117-154]	140[120-168]	0.052
<b>Diastolic blood pressure (mmHg) on arrival</b>	80[68-90]	80[68-90]	82[69-99]	0.249
<b>Heart rate (bpm) on arrival</b>	77[66-90]	75[65-90]	80[70-89]	0.188
<b>Killip classification</b>				
<b>Score≤2</b>	275(91.7)	200(91.7)	75(91.5)	1.000
<b>Score&gt;2</b>	25(8.3)	18(8.3)	7(8.5)	1.000
<b>Arterial access</b>				
<b>Radial</b>	258(86.0)	185(84.9)	73(89.0)	0.850
<b>Femoral</b>	42(14.0)	33(15.1)	9(11.0)	0.462
<b>1-vessel disease</b>	124(41.3)	94(43.1)	30(36.6)	0.546
<b>2-vessel disease</b>	94(31.3)	64(29.4)	30(36.6)	0.432
<b>3-vessel disease</b>	80(26.7)	59(27.1)	21(25.6)	0.888
<b>Culprit vessel</b>				
<b>LMS</b>	6(2.0)	5(2.3)	1(1.2)	0.686
<b>LAD</b>	107(35.7)	86(39.4)	21(25.6)	0.122
<b>LCA</b>	52(17.3)	32(14.7)	20(24.4)	0.135
<b>RCA</b>	116(38.7)	89(40.8)	27(32.9)	0.456
<b>Bypass graft</b>	1(0.3)	1(0.5)	0	1.000
<b>Thrombus aspiration</b>	58(19.3)	45(20.6)	13(15.9)	0.517
<b>Balloon predilatation</b>	243(81.0)	181(83.0)	62(75.6)	0.696
<b>GPI (Tirofiban) use</b>	101(33.7)	79(36.2)	22(26.8)	0.296
<b>Bivalirudin use</b>	6(2.0)	5(2.3)	1(1.2)	0.686
<b>Balloon angioplasty only</b>	16(5.3)	11(5.0)	5(6.1)	0.776
<b>Stent implantation</b>				
<b>DES</b>	250(83.3)	190(87.2)	60(73.2)	0.381
<b>BMS</b>	8(2.7)	8(3.7)	0	0.115
<b>Number of stents **</b>	1.25±0.87	1.33±0.87	1.04±0.85	0.009
<b>Stent diameter &lt;3 mm</b>	87(29)	66(30.3)	21(25.6)	0.477
<b>Door to first device time, min</b>	29[22-35]	29[22-35]	30[21-36]	0.918
<b>Call to first device time, min</b>	99[81-121]	97[79-121]	103[82-121]	0.420
<b>Pain to first device time, min</b>	162[112-235]	160[112-236]	185[118-225]	0.755
<b>Left ventricular function</b>				



<b>Normal (EF ≥55%)</b>	117(39.0)	77(35.3)	40(48.8)	0.188
<b>Mildly impaired (EF 45–54%)</b>	72(24.0)	55(25.2)	17(20.7)	0.556
<b>Moderately impaired (EF 36–44%)</b>	73(24.3)	56(25.7)	17(20.7)	0.556
<b>Severely impaired (EF ≤35%)</b>	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	
<b>ST-segment resolution on ECG pre-PPCI</b>	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
<b>TIMI 2/3 angiographic flow pre-PPCI</b>	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
<b>TIMI 2/3 angiographic flow post-PPCI</b>	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
<b>Peak troponin T (ng/L)</b>	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
<b>Baseline OT (sec) *</b>	400±179	373±202	321±154	559±242	<0.001	414±164	364±146	531±147	<0.001	0.066
<b>Day 2 OT (sec) *</b>	477±132	464±135	455±131	492±148	0.286	483±131	477±123	498±148	0.327	0.254
<b>Baseline LT (sec)</b>	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
<b>Day 2 LT (sec)</b>	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**

<b>Outcome</b>	<b>Whole group (n=300)</b>	<b>Morphine (n=218)</b>	<b>No Morphine (n=82)</b>	<b>P Value</b>
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 $\leq 2$ )	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**



