Impact of prehospital opioid dose on angiographic and clinical outcomes in acute coronary syndromes

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ABSTRACT

Background An adverse interaction whereby opioids impair and delay the gastrointestinal absorption of oral $P2Y_{12}$ inhibitors has been established, however the clinical significance of this in acute coronary syndrome (ACS) is uncertain. We sought to characterise the relationship between prehospital opioid dose and clinical outcomes in patients with ACS.

Methods Patients given opioid treatment by emergency medical services (EMS) with ACS who underwent percutaneous coronary intervention (PCI) between 1 January 2014 and 31 December 2018 were included in this retrospective cohort analysis using data linkage between the Ambulance Victoria, Victorian Cardiac Outcomes Registry and Melbourne Interventional Group databases. Patients with cardiogenic shock, out-of-hospital cardiac arrest and fibrinolysis were excluded. The primary end point was the risk-adjusted odds of 30-day major adverse cardiac events (MACE) between patients who received opioids and those that did not.

Results 10 531 patients were included in the primary analysis. There was no significant difference in 30-day MACE between patients receiving opioids and those who did not after adjusting for key patient and clinical factors. Among patients with ST-elevation myocardial infarction (STEMI), there were significantly more patients with thrombolysis in myocardial infarction (TIMI) 0 or 1 flow pre-PCI in a subset of patients with high opioid dose versus no opioids (56% vs 25%, p<0.001). This remained significant after adjusting for known confounders with a higher predicted probability of TIMI 0/1 flow in the high versus no opioid groups (33% vs 11%, p<0.001).

Conclusions Opioid use was not associated with 30-day MACE. There were higher rates of TIMI 0/1 flow pre-PCI in patients with STEMI prescribed opioids. Future prospective research is required to verify these findings and investigate alternative analgesia for ischaemic chest pain.

Key messages

What is already known on this topic

⇒ A pharmacological interaction exists between opioids and oral $P2Y_{12}$ inhibitors leading to delayed oral bioavailability and antiplatelet effect which may lead to early treatment failure.

⇒ Observational studies assessing the clinical impact of this interaction on adverse outcomes such as recurrent myocardial infarction have demonstrated conflicting results and the clinical impact is currently unclear.

What this study adds

⇒ In this observational study of patients diagnosed with acute coronary syndrome (ACS), no association was seen between opioid use and major adverse cardiac events; however, an association was seen with reduced patency in the culprit coronary artery in patients receiving higher opioid doses.

How this study might affect research, practice or policy

⇒ The investigation of alternative analgesic agents for use in ACS that are safe and effective without interacting with oral $P2Y_{12}$ inhibitors is required.

INTRODUCTION

The medical and interventional management of myocardial infarction (MI) has advanced rapidly leading to a steady decline in age-specific mortality from coronary artery disease. Despite these improvements, heart disease remains at epidemic proportions and a leading cause of death worldwide.[1] In an effort to identify ways of improving clinical outcomes, key aspects of the management of acute MI are being re-evaluated.

Certainly, in the prehospital setting reducing prehospital transfer time and bypassing Emergency Departments (ED) with transfer of patients directly to the cardiac catheterisation laboratory is clearly beneficial.[2–4] Relief of pain in patients with MI however has remained relatively unchanged in over a century. Opioids remain the analgesic agent of choice at least partly due to early studies suggesting beneficial haemodynamic effects through reduced pain-related sympathetic stimulation, venodilatory and vasodilatory effects.[5] Despite this, the clinical benefit of using opioids has little evaluation in prospective randomised studies. Additionally,

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given the subjective nature of pain as experienced by patients and adjudicated by emergency medical staff, dosing of opioids in the prehospital setting is highly variable.[6 7] This is particularly the case for patients with ST-elevation myocardial infarction (STEMI), where patients are more likely to receive intravenous opioids compared with patients with non-ST-elevation myocardial infarction (NSTEMI).[8] Retrospective studies have raised concerns regarding an interaction between opioid analgesia and oral $P2Y_{12}$ inhibitor therapy.[9 10] It is currently unclear from available observational clinical data whether this biochemical interaction leads to worse clinical outcomes or rather that the higher opioid doses reflect an association between more severe pain and a greater proportion of myocardium in jeopardy.[11] It is also unclear whether the haemodynamic benefits of opioids may lead to improved outcomes in patients receiving higher opioid doses.

Using a large dataset of patients with acute coronary syndrome (ACS) that underwent percutaneous coronary intervention (PCI) with comprehensive data linkage between three multicentre databases, this study aims to determine if opioid administration is correlated with an increased risk of adverse angiographic and clinical outcomes across the ACS spectrum.

METHODS

Study population

Patients aged 18 years and over with ACS transported by Ambulance Victoria (AV) to hospital and then undergoing PCI since 2014 identified in the Victorian Cardiac Outcomes Registry (VCOR) and Melbourne Interventional Group (MIG) databases were included in the study. Patients presenting with out-of-hospital cardiac arrest, cardiogenic shock and treated with fibrinolysis were excluded from the analysis. A diagnosis of unstable angina (UA), NSTEMI and STEMI were based on documentation by the treating cardiologist with compatible symptoms meeting American College of Cardiology/American Heart Association (ACC/AHA)-defined UA, NSTEMI and STEMI criteria.[12–14] The study cohort included consecutive patients enrolled in these registries undergoing PCI from January 2014 to December 2018.

Patient and public involvement

The current analysis was undertaken without direct patient involvement.

Registry design

Three sources of data were used. The AV dataset was derived from prehospital electronic patient care records and contains details about prehospital pain scores, analgesic doses and prehospital clinical status. The VCOR is a clinical quality registry including all 32 hospitals in the state of Victoria where PCI is performed and includes baseline, angiographic and outcome data. The third source of data is the MIG research registry. The MIG registry collects procedural and follow-up data on patients undergoing PCI across six public (government funded) hospitals in Victoria, Australia. Patients in MIG (primarily a research registry) are simultaneously included in VCOR. Both the VCOR and MIG registries include baseline characteristics, in-hospital laboratory findings, documentation of coronary lesion type according to ACC/AHA classifications, in-hospital and 30-day outcomes are recorded prospectively using case report forms with standardised definitions for all fields.[13] The Centre of Cardiovascular Research and Education in Therapeutics, School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia is responsible for maintaining and coordinating data collection for these two registries. Internal validity of the data are regularly evaluated by randomly selecting 5% of the records at each institution with review of several verifiable fields.[15] In the most recent audits, a number of fields were assessed with an overall accuracy of 98%, comparable with other large interventional registries internationally.

We created one dataset that linked AV data and the VCOR; a second dataset linked this combined dataset with the MIG registry. Data were linked using three patient identifiers including full name, date of birth and date of hospital arrival.

Data managers of the registries are responsible for collection of 30-day follow-up data. They first review the patient's medical record to see if the patient was re-hospitalised at the same centre. Patients are then contacted directly. This is to confirm the information available in the medical record with respect to the reason for rehospitalisation and any related complications. This information was used to adjudicate 30-day clinical outcomes such as major adverse cardiac events (MACE). If the patient cannot be contacted, data managers obtain follow-up information from the patient's next of kin or general practitioner. Multiple attempts are made. If follow-up data are not available after exhausting all avenues, and no earlier than 6 months after discharge, the patient's status in the registry is recorded as 'lost to follow-up'.

An opt-out consent process is used whereby patients are provided with an information sheet describing the registry, purposes and routine follow-up including review of records and phone contact.

Definitions

MACE are the composite end point of death, non-fatal MI and target vessel revascularisation. Major adverse cardiac and cerebrovascular events (MACCE) are the composite end point of death, non-fatal MI, target vessel revascularisation and stroke. STEMI, NSTEMI and UA were defined as per accepted standard definitions by the ACC.[14 16] Stent thrombosis included combined definite and probable stent thrombosis as defined by the Academic Research Consortium at 30 days.[17] Thrombolysis in myocardial infarction (TIMI) score was defined as per accepted standard definitions by the ACC.[18]

As per current practice guidelines, opioid analgesia is primarily administered by AV for ischaemic chest pain relief. Total opioid dose was categorised as low if ≤8.75 mg of intravenous morphine equivalent, intermediate if between 8.76 and 15 mg intravenous and high if >15 mg. These specific cut-offs were chosen as they approximated equal tertiles for analysis. The current guideline stipulates the use of only two types of opioids, morphine and fentanyl. The routes of opioid administration stipulated are intravenous with intranasal fentanyl only used where timely intravenous access could not be established. For the current analysis, fentanyl dose in micrograms (intravenous or intranasal) was converted into an equivalent intravenous morphine dose by multiplying the total dose by 100. If fentanyl and morphine were both used, then the total fentanyl dose was converted to an equivalent morphine dose and added to the total morphine dose. Oral $P2Y_{12}$ inhibitors are not administered in the prehospital setting as per current AV guidelines. Instead, they are almost universally administered in EDs or in the cardiac catheterisation laboratory in the immediate pre-operative or peri-operative period for all patients treated with PCI.

Study outcomes

The primary end point was 30-day MACE in patients treated with and without opioids. Secondary end points included

pre-PCI TIMI flow rate, and 30-day clinical outcomes such as MACCE stratified by opioid dosing categories.

Recurrent MI was defined as an increase in cardiac biomarkers (troponin T or I, creatine kinase) >5 times the upper limit of normal and/or new significant ST-segment change, development of new Q waves in more than two contiguous electrocardiographic leads or new left bundle branch block pattern.

Study outcomes were adjudicated by data managers for the VCOR and MIG registries based on review of medical records confirmed by phone interview of patients (where available). The process of data collection and adjudication of end points were performed independently without involvement from study investigators.

Statistical analysis

All statistical analyses were performed using SPSS V.22 (IBM).

Variables approximating a normal distribution were summarised as mean±SD and groups were compared using analysis of variance. Non-normally distributed variables were summarised as median and third quartiles (Q1, Q3) and compared using Wilcoxon rank-sum test. Categorical variables were expressed as percentages and compared using χ^2 tests including for trends with post hoc analyses performed using the Bonferroni method. The association between opioid administration and clinical outcomes was assessed using binary logistic regression. This model was adjusted for age, sex, body mass index, diabetes, ACS type, peripheral vascular disease, cerebrovascular disease and culprit vessel for PCI. The results of the logistic regression analysis were reported as adjusted ORs with 95% CIs.

We also undertook a post hoc exploratory analysis evaluating the correlation between prehospital opioid dosing and initial pain score severity using Spearman's rank correlation in the MIG registry of patients with STEMI undergoing PCI. In the subset of patients with STEMI, binary logistic regression was used to adjust for potential confounding factors when evaluating the association between total prehospital opioid administration and TIMI 0/1 flow pre-PCI as a marker of poor culprit artery patency. This model adjusted for age, sex, diabetes, history of MI, smoking history, culprit vessel and initial pain score severity. $P2Y_{12}$ inhibitor use was not included in the multivariate model as $P2Y_{12}$ inhibitor use was near universal (>99%) in our dataset. This model was then used to calculate the predicted probability of TIMI 0/1 flow pre-PCI in each opioid dosing category while holding all other covariates at their mean values (eg, marginal effect at the mean).

RESULTS

A total of 10 531 patients were included in the primary analysis, using the data linkage between AV and VCOR databases. Data on the primary end point of 30-day MACE was available for all 10 531 patients. There were 1123 (11%) patients with a diagnosis of UA, 4541 (43%) patients with NSTEMI and 4867 (46%) patients with a diagnosis of STEMI (figure 1). There were 3878 patients that received no opioids, 2943 patients receiving low-dose opioids, 2211 with intermediate-dose opioids and 1499 with high-dose opioids. Patients receiving no opioids were significantly older, less likely to be male and more likely to have comorbidities such as diabetes, peripheral vascular disease and prior coronary intervention compared with patients with high-dose opioid administration (table 1). The median opioid dose in the low-opioid, intermediate-opioid and high-opioid categories were 5 mg, 10 mg and 20 mg of intravenous morphine equivalent dose, respectively.

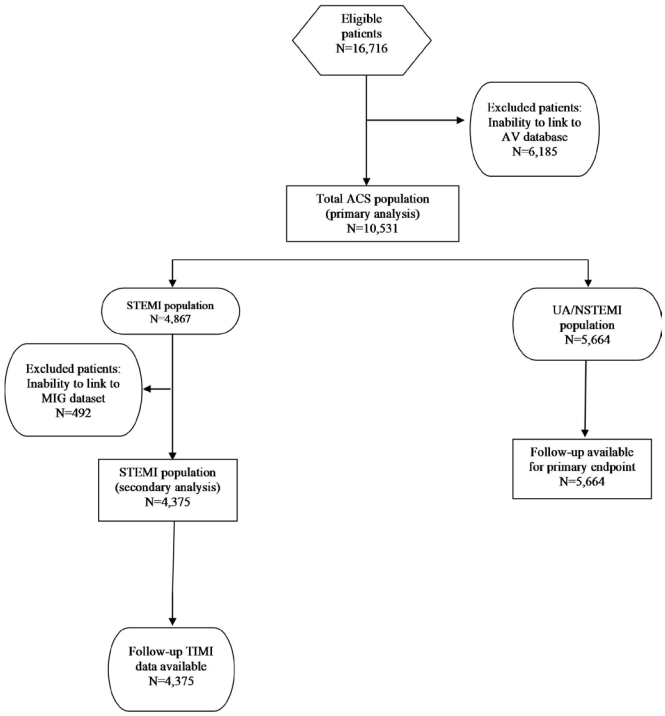

Figure 1 Study Standards for Reporting Diagnostic accuracy studies (STARD) flow chart. Depicts the study population with respect to data linkage including the reporting of patient exclusion and follow-up. ACS, acute coronary syndrome; AV, Ambulance Victoria; MIG, Melbourne Interventional Group; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction; UA, ustable agina.

Median initial pain scores were significantly higher in the high-dose opioid group compared with the no opioid group (numerical rating scale, 8 vs 4, p<0.001). The median final pain score was also higher in the high-dose opioid group compared with the no opioid group (3 vs 0, p<0.001). Median pain reduction was greater in the high-dose opioid compared with the no opioid group (4 vs 3, p<0.001).

Outcomes

Clinical outcomes

The primary end point of 30-day MACE was not significantly different between high dose versus no opioid groups (3.5% vs 4.3%, p=0.27; see table 2 for 30-day clinical outcomes).

After adjustment, for key covariates, 30-day MACE, all-cause mortality, MACCE and stent thrombosis remained non-significant between patients in the opioid and no opioid groups (figure 2).

Angiographic characteristics

Of the 4867 with STEMI, angiographic characteristics for 4375 patients could be obtained. There was greater use of radial access in the high-dose opioids group compared with the no opioid group (63% vs 54%, p=0.003, see table 3). There was also greater use of glycoprotein (GP) IIb/IIIa inhibitors in the high-dose opioid group compared with the no opioid group (39% vs 26%, p<0.001) and greater use of thrombus aspiration in the intermediate-dose opioid group compared with the no opioid group (17% vs 13%, p<0.001). $P2Y_{12}$ inhibitor use was near universal (>99%) and there were no significant differences in aspirin administration between the groups.

Table 1 Baseline characteristics n=10 531

Baseline characteristics	No opioids N=3878	Low-dose opioids N=2943	Intermediate-dose opioids N=2211	High-dose opioids N=1499	P value comparing no opioids with high dose
Age in years, mean (SD)	69 (13)	66 (13)	64 (12)	61 (12)	<0.001
Male, n (%)	2690 (69)	2167 (74)	1717 (78)	1184 (79)	<0.001
Diabetes, n (%)	924 (24)	594 (20)	385 (17)	274 (18)	<0.001
BMI (IQR) N=10 346	27.7 (24.6–31.2)	27.5 (24.5–30.9)	27.7 (24.7–30.9)	28.4 (25.5–32)	<0.001
PVD, n (%)	178 (4.6)	83 (2.8)	75 (3.4)	41 (2.7)	<0.001
Cerebrovascular disease, n (%)	192 (5)	109 (3.7)	87 (3.9)	60 (4)	0.055
Previous PCI, n (%)	920 (24)	599 (20)	404 (18)	284 (19)	<0.001
Previous CABGs, n (%)	307 (7.9)	192 (6.5)	88 (4)	58 (3.9)	<0.001
ACS type, n (%)					<0.001 % are rows
UA	644 (57)	309 (28)	112 (10)	58 (5.2)	
NSTEMI	2444 (54)	1218 (27)	575 (13)	304 (6.7)	
STEMI	790 (16)	1416 (29)	1524 (31)	1137 (23)	
Initial pain score numerical rating scale (median, IQR) N=10 514	4 (2, 6)	6 (4, 8)	7 (5, 8)	8 (6, 8)	<0.001
Final pain score numerical rating scale (median, IQR) N=10 203	0 (0, 2)	1 (0, 3)	2 (1, 4)	3 (1, 5)	<0.001
Pain reduction numerical rating scale (median, IQR) N=8521	3 (1, 5)	4 (2, 5)	4 (2, 6)	4 (2, 6)	<0.001
Opioid dose median dose in mg (IQR)	0	5 (2.5, 7.5)	10 (10, 15)	20 (20, 25)	<0.001
EF grade N=9524					<0.001
Normal n (%)	2182 (64)	1445 (55)	991 (49)	635 (45)	
Mild n (%)	674 (20)	702 (27)	612 (30)	418 (30)	
Moderate n (%)	393 (12)	372 (14)	338 (17)	256 (18)	
Severe n (%)	171 (5)	131 (4.9)	98 (4.8)	90 (6.4)	

N is number of patients with data available for variable if less than total sample population.
ACS, acute coronary syndrome; BMI, body mass index; CABG, coronary artery bypass graft surgery; EF, ejection fraction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; STEMI, ST-elevation myocardial infarction; UA, unstable angina.

There were significantly more patients with TIMI 0 or 1 flow pre-PCI in patients in the high-dose versus no opioid groups (56% vs 25%, p<0.001, see table 3). There was also a higher proportion of patients with poor culprit artery flow (TIMI 0 or 1) comparing patients not administered opioids with those administered low, intermediate and high doses. Procedural success and no reflow was not significantly different between the groups.

In the exploratory analysis, there was a moderate correlation (Spearman's rho=0.58) between initial pain score severity and dose of opioid administered to patients with STEMI which was highly significant (p<0.001) between these two variables (see online supplemental figure 1).

The unadjusted OR for TIMI flow 0 or 1 pre-PCI in patients receiving opioids was 3 (95% CI 2.6 to 3.4, p<0.001). After adjustment for key covariates, including initial pain score severity, the adjusted OR was 2.7 for patients receiving opioids (95% CI 2.3 to 3.2, p<0.001). Additionally, the predicted probability of TIMI 0 or 1 flow pre-PCI stratified by opioid dosing category was calculated after adjusting for the same

Table 2 30-day clinical outcomes n=10 531

Clinical end points	No opioids N=3878	Low-dose opioids N=2943	Intermediate-dose opioids N=2211	High-dose opioids N=1499	P value comparing no opioids with high dose
MI n (%) N=10 292	49 (1.3)	51 (1.7)	26 (1.2)	18 (1.2)	0.247
Major bleeding, n (%)	55 (1.4)	43 (1.5)	32 (1.4)	26 (1.7)	0.852
Stroke, n (%) N=10 269	31 (0.8)	10 (0.3)	9 (0.4)	8 (0.5)	0.054
MACE, n (%)	167 (4.3)	139 (4.7)	104 (4.7)	53 (3.5)	0.266
MACCE, n (%)	192 (5)	148 (5)	112 (5.1)	60 (4)	0.418
Stent thrombosis, n (%)	20 (0.5)	19 (0.6)	19 (0.9)	15 (1)	0.186

N is number of patients with data available for variable if less than total sample population.
MACCE, major adverse cardiovascular and cerebrovascular events; MACE, major adverse cardiac events; MI, myocardial infarction.

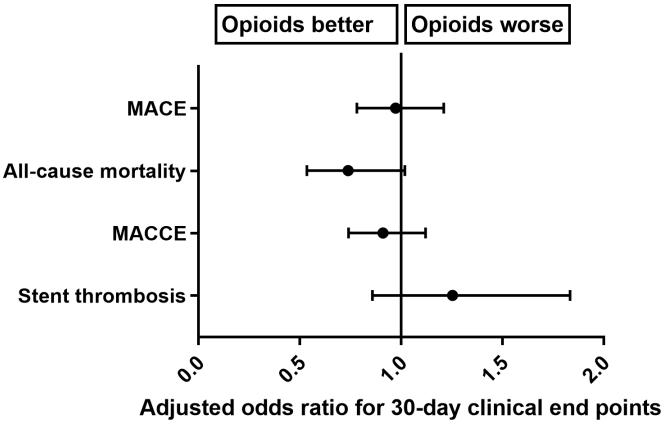

Figure 2 Forest plot with adjusted ORs for 30-day clinical end points in relation to opioid use. Dot points represent OR estimate for each end point defined on y-axis. Error bars represent 95% CI. An OR <1 represents decreased risk of clinical end point, an OR >1 represents an increased risk of clinical end point. All p values >0.05. MACE, major adverse cardiac event; MACCE, major adverse cardiac and cerebrovascular event. Adjusted ORs derived using binary logistic regression model adjusting for the following potential confounding factors: age, sex, body mass index, diabetes, acute coronary syndrome type, peripheral vascular disease, cerebrovascular disease and culprit vessel with intervention.

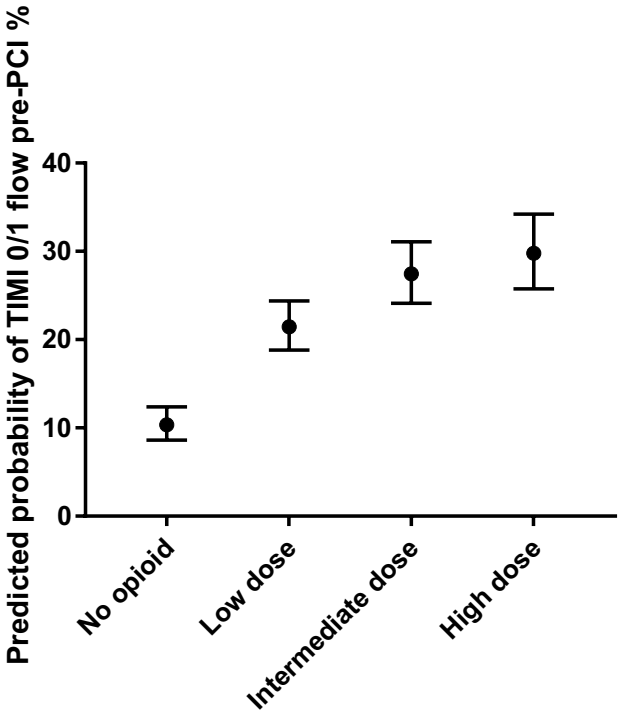

Figure 3 Predicted probability of pre-PCI TIMI 0 or 1 flow in culprit artery in STEMI subset stratified by opioid dose. Predicted probability of pre-PCI TIMI 0/1 flow in culprit artery in STEMI subset represented on the y-axis as a percentage. This was derived by adjusting for age, sex, diabetes, history of myocardial infarction, smoking history and culprit vessel using binary logistic regression. Opioid dosing categories as previously defined; low dose ≤8.75 mg, intermediate dose 8.76–15 mg and high dose >15 mg of intravenous morphine equivalent dose. PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction.

covariates used in the binary logistic regression model. After adjustment there was a significantly higher predicted rate of pre-PCI TIMI 0 or 1 flow in the low-opioid, intermediate-opioid and high-opioid dosing categories compared with no opioids (see figure 3).

DISCUSSION

Our study identified no significant differences in 30-day MACE between patients treated with opioids and those that were not, after adjustment for potential confounding factors. We did identify a greater proportion of patients with TIMI 0 or 1 flow in the culprit coronary artery pre-PCI in patients receiving higher opioid doses and this remained significant after adjusting for potential confounding factors.

We also found a moderate correlation between initial chest pain severity and opioid dose administered, suggesting paramedics titrated opioid dose administered to the degree of pain reported. However, opioids remained an independent predictor

Table 3 Interventional characteristics in a STEMI subset n=4375

Variable	No opioids N=1400	Low-dose opioids N=1301	Intermediate-dose opioids N=1033	High-dose opioids N=641	P value comparing no opioids with high dose
TIMI flow pre 0 or 1, n (%)	350 (25)	568 (44)	546 (53)	356 (56)	<0.001
Procedure success, n (%)	1357 (95)	1234 (95)	987 (96)	622 (97)	0.143
Transient No reflow, n (%)	31 (2.2)	32 (2.5)	26 (2.5)	12 (1.9)	0.574
Persistent No reflow, n (%)	8 (0.6)	13 (1)	9 (0.9)	2 (0.3)	0.574
Radial access, n (%)	756 (54)	755 (58)	620(60)	404 (63)	<0.003
GP IIB/IIIA, n (%)	364 (26)	429 (33)	403 (39)	250 (39)	<0.001
Thrombus aspiration, n (%)	182 (13)	182 (14)	176 (17)	96 (15)	<0.001 comparing no opioids with intermediate dose
Rotational atherectomy, n (%)	0	1 (0.1)	1 (0.1)	1 (0.2)	0.78
Mechanical ventricular support, n (%)	14 (1)	5 (0.4)	7 (0.7)	2 (0.3)	0.099
$P2Y_{12}$ Inhibitor	1393 (99.5)	1297 (99.7)	1030 (99.7)	640 (99.8)	0.87
Aspirin	1358 (97)	1275 (98)	1002 (97)	635 (99)	0.21
OAC	126 (9)	104 8)	103 (10)	51 (8)	0.09

GP IIB/IIIA, glycoprotein IIB/IIIA inhibitor; OAC, oral anticoagulant; STEMI, ST-elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction.

of poor culprit artery antegrade flow even when initial chest pain severity was included in the binary logistic regression model.

All routes of opioid administration have been shown to delay the therapeutic antiplatelet action of all oral $P2Y_{12}$ inhibitors by causing gastroparesis and impaired gastrointestinal motility.[19–21] The clinical relevance of this interaction, however has been more challenging to elucidate due to significant confounding factors in all observational studies.[8 9 22 23]

Prior clinical trials have had conflicting results relating to whether opioid administration is detrimental or beneficial related to clinical outcomes, which likely reflect an imbalance of baseline characteristics between patients administered opioids and those that were not.[8] In a prior retrospective study of patients with STEMI, we identified an association between opioid dose and myocardial infarct size based on creatine kinase.[24] However, in that study, opioid administration was nearly universal and therefore comparison with patients not administered opioids was not possible.

The present study differs from prior observational studies in the availability of accurate prehospital opioid dosing, enabling a comparison of patients without opioid administration and those with low and intermediate opioid dosing. Overall, it suggests that while opioids may interfere with the onset of platelet inhibition by $P2Y_{12}$ inhibitors with consequent angiographic complications and compromised perfusion in the infarct-related artery, this is not associated with worse 30-day clinical outcomes. This disparity between angiographic and clinical outcomes may explain the conflicting results in prior observational studies evaluating this interaction. Indeed, the Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery (ATLANTIC) study also found that in patients administered opioids, the reduction in ST-segment elevation seen with prehospital $P2Y_{12}$ loading was lost, suggesting early treatment failure.[25] In that study, there was a reduction in early stent thrombosis with prehospital ticagrelor loading, but no significant difference in MACE at 30 days.

In the current study, patients with STEMI were more likely to be in the high opioid dose group, and this group also had higher rates of thrombus aspiration catheter use and GP IIB/IIIA inhibitor use. This may reflect the higher acuity ACS presentation rather than being related to opioid use. Ultimately, a randomised trial is required to determine if opioids are causative in leading to early antiplatelet treatment failure and greater thrombotic complications or are simply associated with greater thrombotic burden leading to greater ischaemic pain.[26]

Clearly, an alternative analgesic agent to opioids that is safe and effective in treating chest pain related to MI will be required for any planned prospective randomised trial. Importantly, studies are underway internationally to evaluate alternative analgesic agents. For example, the recently published ON-TIME 3 study suggests intravenous acetaminophen is as effective as opioids for ischaemic chest pain.[27] Additionally, our group has completed recruitment for a prehospital study testing intravenous lidocaine in suspected STEMI as an alternative analgesic agent to opioids (ACTRN12619001521112p).[26]

Limitations

There are several limitations of our study. As an observational study, the lack of randomisation in allocation of opioid therapy may be responsible for an imbalance of confounding factors between the groups, despite statistical adjustment for measurable confounders. Additionally, while there is excellent record keeping for administration of opioid dosing in the prehospital setting, we do not have data relating to in-hospital opioid administration.

Additionally, the decision to refer a patient for coronary angiography and perform PCI was at the discretion of the treating cardiologist and cardiology team. Unfortunately, we do not have data relating to the rationale for this decision or timing of PCI in patients with NSTEMI or UA.

Finally, while the proposed mechanism of impaired TIMI flow pre-PCI is the delayed onset and activity of oral $P2Y_{12}$ inhibitors, we do not have information on timing of oral $P2Y_{12}$ inhibitors during index admission, loading dose used or results of platelet function testing results to support this mechanism. However, previous biochemical studies have demonstrated that opioid analgesia delays the onset of action of all oral $P2Y_{12}$ inhibitors in patients with acute MI.[19]

The present study identified no association between opioid use and MACEs in patients with ACS. There was however an association between reduced patency in the culprit coronary artery with increasing opioid utilisation. Randomised trials are required to definitively determine the clinical significance of the opioid-$P2Y_{12}$ inhibitor interaction and to confirm the findings of our study. In the meantime, studies evaluating strategies to mitigate this interaction as well as investigating safe, effective alternative analgesics to opioids are needed.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Separate, specific ethics review and approval was gained for this specific study by The Alfred Hospital Human Research and Ethics Committee (ref. 651/19). The ethics committee in each hospital have approved the MIG and VCOR registries.

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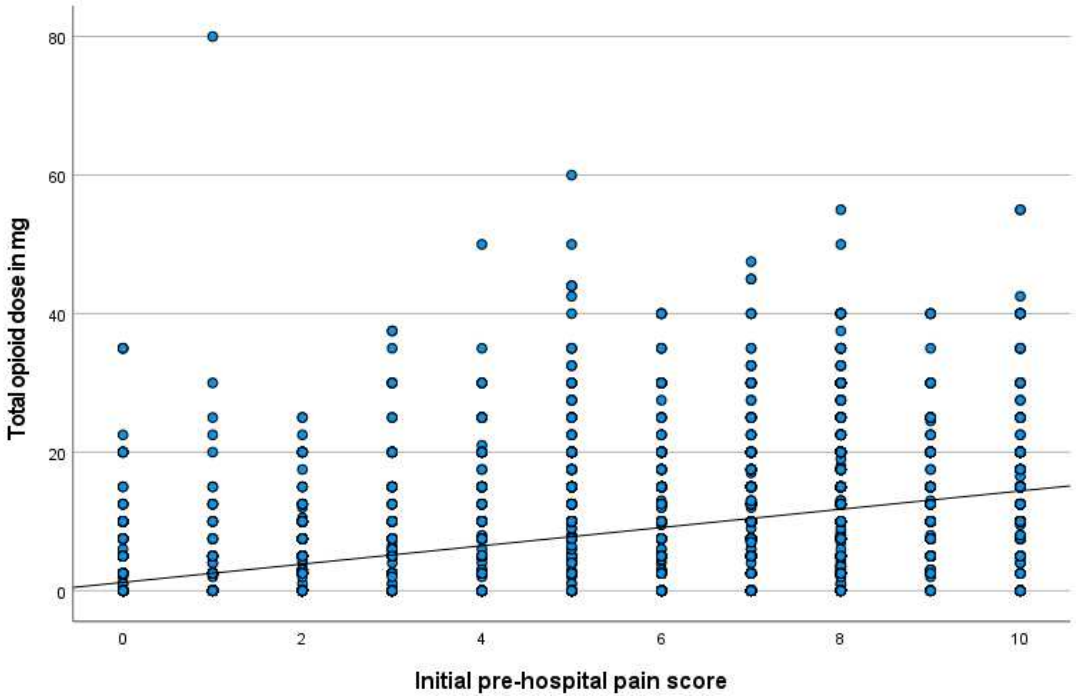
Supplementary material

Table 1 – Binary logistic regression analysis of clinical outcomes – no opioids given as reference group

30-day outcome	**Unadjusted odds ratio (95% CI)**	**P value**	**Adjusted odds ratio (95% CI)**	**P value**
MACE	1.035 (0.852,1.256)	0.73	0.973 (0.782,1.211)	0.808
All-cause mortality	0.8 (0.606,1.058)	0.118	0.738 (0.535,1.018)	0.064
MACCE	0.97 (0.807,1.165),	0.745	0.911 (0.741, 1.121)	0.38
Stent thrombosis	1.549 (0.925,2.595)	0.096	1.254 (0.858,1.834)	0.243

MACE = major adverse cardiac events, MACCE = major adverse cardiovascular and cerebrovascular events, CI = confidence interval



Supplementary Figure 1: Scatter plot demonstrating relationship between initial prehospital pain score (numerical rating scale) on x-axis and total prehospital opioid dose in mg on y-axis with line of best fit; Spearman's rho = 0.58, p<0.001