Impact of pre-admission morphine on re-infarction in patients with STEMI treated with PPCI: a meta-analysis

Ying X. GUE MB BS, MRCP [1,2], Nikolaos SPINTHAKIS MD [1,2], Mohamed FARAG MB BS, MRCP, PhD [1,3], Jacek KUBICA MD, PhD [4], Jolanta M. SILLER-MATULA MD, PhD [5], Manivannan SRINIVASAN MB BS, MD, FRCP [2], Diana A. GOROG MB BS, MD, PhD, FRCP [1,2,6]

1. Department of Postgraduate Medicine, University of Hertfordshire, Hertfordshire, United Kingdom
2. Cardiology Department, Lister Hospital, East and North Hertfordshire NHS Trust, Stevenage, United Kingdom
3. Cardiology Department, Royal Papworth Hospital NHS Foundation Trust, Papworth Everard, Cambridge, United Kingdom
4. Department of Cardiology and Internal Medicine, Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland
5. Division of Cardiology, Department of Medicine II, Medical University of Vienna Austria
6. National Heart & Lung Institute, Imperial College, London, United Kingdom

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Corresponding author: Prof. Diana A Gorog, d.gorog@imperial.ac.uk
National Heart & Lung Institute,
Imperial College, Dovehouse Street,
London SW3 6LY, United Kingdom
Tel: +44 (0) 207 034 8934

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Abstract

Opiates are the traditional analgesics used for pain relief in patients with ST-elevation myocardial infarction (STEMI). Pharmacodynamic studies indicate that opiates delay the absorption of orally-administered $P2Y_{12}$ inhibitors and the onset of platelet inhibition. Whether the negative effect of opiates on platelet inhibition impacts on clinical outcomes is unclear.

A systematic review and meta-analysis was performed searching PubMed, MEDLINE and Cochrane Central Register of Controlled Trials to identify studies comparing morphine and no-morphine treatment in STEMI patients undergoing primary percutaneous coronary intervention (PPCI). The primary endpoint was the occurrence of in-hospital recurrent myocardial infarction, and secondary endpoints included in-hospital stroke and death.

Four observational studies, including a total of 3220 patients, were identified. Amongst patients with STEMI, those treated with morphine had a higher rate of re-infarction compared to patients not receiving morphine (1.5% vs. 0.67%, odds ratio [OR] 2.41; 95% confidence interval [CI] 1.11-5.21; p=0.03). Mortality rate was lower in morphine-treated patients (1.7% vs. 4.2%, OR 0.43, 95% CI 0.23-0.81; p=0.009). There was no difference in stroke according to morphine treatment.

Patients undergoing PPCI who are pre-treated with morphine have a higher rate of re-infarction than patients not receiving morphine. This may be attributable to opiate-related delay in $P2Y_{12}$ inhibitor absorption and resultant delay in onset of platelet inhibition. These concerning findings indicate the need for prospective, randomised trials to assess the impact of opiates on clinical outcomes in STEMI.

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59 # Abbreviations

60

61	ACS	Acute coronary syndrome
62	GPI	Glycoprotein IIb/IIIa inhibitor
63	MACE	Major adverse cardiovascular event
64	MRI	Magnetic resonance imaging
65	NSTEMI	Non-ST-elevation myocardial infarction
66	PCI	Percutaneous coronary intervention
67	PPCI	Primary percutaneous coronary intervention
68	STEMI	ST-elevation myocardial infarction

Introduction

Morphine is the traditional analgesic mainstay for patients presenting with ST-elevation myocardial infarction (STEMI) and has been used in this setting for >100 years. Whilst opiates continue to be used to relieve the symptoms of chest pain, without evidence base, the other treatment strategies for STEMI have significantly evolved, through the use of primary percutaneous coronary intervention (PPCI) to establish epicardial flow and the need to minimise re-occlusion and stent thrombosis through the use of potent $P2Y_{12}$ inhibitors[1]. However, concerns have arisen in the last few years about the potential adverse effects of morphine in the setting of acute coronary syndrome (ACS), where it may delay the absorption of orally-administered $P2Y_{12}$ inhibitors and potentially result in delayed onset of $P2Y_{12}$ inhibitor-mediated platelet inhibition[2,3].

The CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the American College of Cardiology/American Heart Association Guidelines) registry[4] was one of the first to report a possible negative effect of morphine administration in ACS. Subsequently, a number of studies evaluating the effect of morphine on clinical outcomes in patients with ACS have shown that morphine delays and attenuates the effect of oral $P2Y_{12}$ inhibitors[5–7]. The Platelet Aggregation with Ticagrelor Inhibition and Fentanyl (PACIFY) randomized trial showed that fentanyl, in the same way as morphine, delayed the absorption and action of oral ticagrelor loading in patients undergoing percutaneous coronary intervention (PCI), evidenced by reduced platelet inhibition, indicating that this is likely to be a class effect[8]. Based on these and other studies, the European Society of Cardiology (ESC)[1] and the American College of Cardiology Foundation/American Heart Association (ACCF/AHA)[9] have downgraded the level of evidence for the use of intravenous opioids in the setting of STEMI from level I to level IIa.

95 However, it is unclear whether the observed effect of opiates on platelet inhibition is simply a
96 laboratory phenomenon without clinical sequelae, or whether the effects directly translate
97 into an adverse effect on clinical outcomes is unclear, with small observational studies
98 showing varying impact on hard clinical endpoints such as death and reinfarction[10–12]. The
99 potential adverse impact of opiates on $P2Y_{12}$ inhibitor effects is likely to be of greatest
100 significance in the setting of STEMI, yet no prospective randomised trials have addressed
101 this.
102 Therefore, it was our aim to evaluate the current evidence base in the literature to determine
103 the impact of opiates, in particular morphine or diamorphine, on in-hospital clinical outcomes
104 in the setting of STEMI, and in particular in patients undergoing PPCI.
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106
107 ## Methods
108
109 We performed a systematic review and meta-analysis of studies assessing the impact of
110 morphine administration on clinical outcomes and cardiac enzymes in patients presenting
111 with STEMI and treated with PPCI. Our work complies with the recommendations in the
112 consensus statement outlined by the Meta-analysis of Observational Studies in Epidemiology
113 group[13].
114
115 *Search strategy*
116 We performed a systematic search of online databases PubMed, MEDLINE and Cochrane
117 Central Register of Controlled Trials up until June 2019 for studies comparing morphine and
118 no-morphine treatment in patients with STEMI treated with PPCI. The search strategy was
119 broad and included the following keywords separately and in combination: “morphine”,
120 “opioids”, “opiates”, “PCI”, “PPCI”, “STEMI”, “myocardial infarction”, and “ACS”, and we
121 restricted the search to full length articles published in the English language and in peer-

reviewed journals. Abstracts were screened for suitability and relevant studies retrieved. In an attempt to identify all studies, references of relevant manuscripts were searched for additional studies not identified from the initial database search. Two reviewers (Y.G. and N.S.) independently performed the search and literature screen, with disputes resolved by consensus following discussion with a third author (D.A.G.).

The PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses)[14] guidelines for reporting systematic reviews and meta-analyses.

Inclusion and exclusion criteria

The following inclusion criteria were applied: 1) studies comparing morphine or opioids to no opioids, 2) observational or randomised, 3) reporting on patients with STEMI undergoing PPCI, 4) follow-up data available up to at least the end of index hospital stay, 5) reporting in-hospital clinical outcomes that included myocardial infarction, stroke and death.

The following studies were excluded: 1) non-English language studies, 2) only abstract available, 3) not reporting outcome of interest. Definitions of outcomes in each of the included studies are detailed in supplementary material [Supplemental Table 1]. Selected trials were compared, and disagreement was resolved by team discussion and consensus.

Endpoints

Our primary outcome of interest was the occurrence of recurrent myocardial infarction in hospital. Secondary outcomes of interest were in-hospital death and stroke.

Data Extraction

Data were independently extracted from relevant published articles by two authors (Y.G. and N.S.) after determining their eligibility for inclusion. Data extracted included baseline patient

147 characteristics, treatment of STEMI, medications in particular antiplatelet and anticoagulant
148 treatment, and clinical outcomes.
149
150 *Statistical analysis*
151 Pooled odds ratios (OR) with 95% confidence interval (CI) were estimated for binary
152 variables using a random-effects model with the method of DerSimonian and Laird[15].
153 Heterogeneity between individual studies was explored by X^2 statistic and characterized with
154 I^2 statistic. All analyses were performed using RevMan Version 5.3.5 software (The Nordic
155 Cochrane Centre, The Cochrane Collaboration, 2014).
156
157 Included studies were assessed using the Risk of Bias in Non-randomized Studies of
158 Interventions (ROBINS-I) tool, which considers biases from confounding, selection of
159 participants into the studies, missing data, and measurement of outcomes[16]. Tests for
160 publication bias were not performed since less than 10 studies were included in the analysis.
161 Results were reported in accordance with the PRISMA guideline[14].
162

Results

Our initial search screen yielded a total of 663 potential articles, of which 25 full text articles were retrieved and reviewed for inclusion (Figure 1). Of these, 2 studies were excluded since only infarct size, based on cardiac MRI, was reported as an outcome[17,18], a further study was excluded since it included a mixed group of patients with both STEMI and non-ST elevation ACS where STEMI data could not be extricated[7], and another study excluded as it included only patients with non-ST elevation ACS[4]. A further 17 studies were excluded for not reporting the clinical outcome of interest[5,8,10,19–32].

Four publications (5 studies) involving a total of 4946 patients with STEMI were identified as suitable for inclusion[6,11,12,33] (Figure 1). One publication, the French Registry of Acute ST-elevation and non-ST- elevation Myocardial Infarction (FAST-MI) programme[11], reported data from 2010 and additional data from another observational study in 2005 within the paper. However, as there were few patients within the FAST-MI 2005 cohort who were treated with PCI (35.1% of entire cohort) and since 27.4% of those patients were treated with pre-hospital fibrinolysis, we felt the cohort of FAST-MI 2005 was significantly different to the cohorts of other studies in the analysis, where PPCI was the default strategy. In particular, the pre-hospital fibrinolysis would have likely negated any adverse effect of the morphine-$P2Y_{12}$ inhibitor interaction. Hence, we excluded FAST-MI 2005 from the main analysis.

The characteristics of the studies included in the analysis are detailed in Table 1 and definition of outcomes in the studies in Supplementary Table 1. Baseline clinical characteristics of patients in both treatment arms are shown in Table 2. In the FAST-MI 2010 study, patients treated with morphine were significantly lower risk, being younger, with lower GRACE score and lower prevalence of diabetes, hypertension and left ventricular

187 impairment than patients not receiving morphine. In the other three studies, patients in the
188 morphine and no-morphine groups were well matched for clinical characteristics.
189
190 Amongst patients with STEMI, those treated with morphine had a higher rate of re-infarction
191 compared to patients not receiving morphine (1.5% vs. 0.67%, OR 2.41; 95% CI 1.11-5.21;
192 p=0.03) (Figure 2 and Figure 3). Mortality rate was lower in morphine-treated patients (1.7%
193 vs. 4.2%, OR 0.43, 95% CI 0.23-0.81; p=0.009). There was no difference in stroke according
194 to morphine treatment. Sensitivity analysis with exclusion of data from FAST-MI showed the
195 difference in in-hospital re-infarction rate (1.3% vs 0.5%, OR 2.02; 95% CI 0.39-10.43;
196 p=0.40) and mortality (2.07% vs 3.04%, 95% CI 0.28-1.99; p=0.56) was no longer
197 significant.
198
199 Trial quality was assessed using the ROBINS-I tool and is shown in Supplemental Table 2.
200 As all the studies were observational cohort studies, the potential for confounding of the
201 effect of morphine cannot be underestimated and would therefore provide bias towards all the
202 studies. The studies by Bellandi *et al.* and Parodi *et al*. had some selection bias due to the
203 presence of predefined exclusion criteria whilst the other studies included consecutive
204 unselected patients. The comparison groups were clearly defined in all the studies and
205 outcome data of interest were provided for all participants within each study. The overall risk
206 of bias is low in the studies included.
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Discussion

The main finding of our study is that patients with STEMI treated with morphine appear to have a higher rate of early reinfarction than patients treated without morphine.

Prior publications show that there is an important pharmacodynamic interaction between opiates and $P2Y_{12}$ inhibitors. Opiates, such as morphine and fentanyl, appear to delay the onset of effect and reduce the maximal platelet inhibition achieved by oral $P2Y_{12}$ inhibitors (clopidogrel, ticagrelor, prasugrel) in patients with ACS,[5,24,33,34] by reducing gastrointestinal absorption[35]. In an elegant cross-over trial in patients with stable coronary artery disease, morphine, compared to saline, significantly delayed prasugrel absorption and delayed the onset of adequate platelet inhibition[22]. However, the clinical impact of this pharmacodynamic interaction is less well understood, and there have been no prospective randomised trials comparing clinical outcomes of patients with STEMI treated with morphine and without morphine. Our study provides evidence that the morphine-$P2Y_{12}$ inhibitor interaction may have more than just pharmacodynamic impact, and may have important adverse clinical consequences.

Reinfarction within the first few days after PPCI for STEMI is usually attributable to stent thrombosis. The aetiology of this relates to patient-related, lesion-related, procedural, and post-procedural factors[36]. These factors predispose to stent thrombosis generally by triggering a recurrent or persistent prothrombotic state attributable to exposure of blood to stent struts, and/or polymer material, leading to activation of the extrinsic pathway of the coagulation cascade, persistent slow coronary flow and low shear stress leading to activation of the intrinsic pathway or inadequate pharmacological suppression of platelet activation.

The role of suboptimal platelet inhibition as a contributor to early stent thrombosis is well recognised. A large-scale meta-analysis of 221,066 patients with 4,276 episodes of stent thrombosis, reported early DAPT discontinuation amongst the 3 most consistently reported

predictors of stent thrombosis[37]. Sub-group analysis of patients in the PLATO trial treated with PPCI revealed that stent thrombosis occurred significantly less often in ticagrelor- than in clopidogrel-treated patients[38] and the role of potent platelet inhibition in reducing stent thrombosis is further supported by the observation that glycoprotein IIb/IIIa inhibitor (GPI) treatment in ACS reduces acute stent thrombosis compared with heparin alone[39,40].

In addition to the studies reported here, the potential adverse clinical impact of a morphine-$P2Y_{12}$ inhibitor interaction is supported by a study in 276 STEMI patients treated with PPCI, in which morphine use was an independent predictor of larger infarct size on cardiac MRI[18] and an observational study of nearly 1000 patients with anterior STEMI, showing a non-significant trend towards a higher rate of recurrent MI in patients treated with, compared to those not treated with, morphine (3.8% vs. 1.7%, p=0.08)[27].

Baseline differences in clinical characteristics between STEMI patients treated with morphine and without morphine, could underlie the difference in mortality between the morphine and no-morphine groups in our meta-analysis. In the largest study included in this analysis, the FAST MI 2010 study, patients receiving morphine were significantly lower risk, with significantly lower age, lower prevalence of cardiovascular risk factors, and lower GRACE score than patients treated without morphine[11]. Meta-regression analysis of the baseline characteristics did not show any significant correlation with in-hospital mortality. However, as patient-level data was unavailable, we could not perform further analysis to adjust for the clinical difference.

The study by Parodi *et al.*[33] did not report time from onset of symptoms to PPCI, whilst in the studies of Farag *et al.*[12] and Bellandi *et al.*[6] the symptom-to-balloon time was similar in the morphine and no-morphine groups, whereas in the FAST-MI 2010 study,[11] patients not receiving morphine had significantly longer time from symptom onset to revascularization, that may have impacted on outcome in this cohort. Our findings are supported by the recently

263 published ATLANTIC-Morphine study[41]. In this retrospective analysis of 1862 patients with
264 STEMI who received ticagrelor 180 mg with (49%) or without (51%) concomitant morphine
265 in the ATLANTIC study, morphine-treated patients less often had pre-PPCI TIMI 3 flow,
266 were more frequently given GPI and more frequently underwent mechanical thrombus
267 aspiration, suggestive of larger thrombus burden, than patients who did not receive
268 morphine[41]. Furthermore, morphine-treated patients tended to be younger, with shorter time
269 from symptom onset to ECG diagnosis and treatment, which is an important determinant of
270 prognosis. The shorter time to diagnosis and greater GPI use may have ameliorated the
271 adverse effects of the morphine-$P2Y_{12}$ inhibitor interaction.
272 Interestingly, addition of FAST-MI 2005 data into the analysis showed that in-hospital
273 mortality remained significant in favour of morphine whilst re-infarction was no longer
274 significant [Supplement Figure 1]. This may reflect non-contemporaneous data where there
275 was lesser PPCI but could also reflect the protective impact of fibrinolysis negating the
276 impact of morphine on platelet inhibition.
277 Our findings lend support to the concept that non-opioid analgesics such as intravenous
278 paracetamol should be considered to relieve pain in STEMI patients, in order to mitigate
279 against the effects of the opiate-$P2Y_{12}$ inhibitor interaction. The SCADOLII (Comparison of
280 MEOPA [nitrogen monoxide-oxygen mixture] plus Paracetamol Versus Morphine Treatment
281 in Acute Coronary Syndrome Analgesia) randomised trial (NCT02198378) will provide
282 valuable insight into the use of non-opioid analgesia in the setting of STEMI.

283 If opioids are used, consideration should be given to maximal concomitant $P2Y_{12}$ inhibition
284 through the use of the intravenous $P2Y_{12}$ inhibition cangrelor[2,34] or through the use of
285 additional parenteral antithrombotic agents such as GPI[2,31,34]. Newer $P2Y_{12}$ inhibitors given
286 subcutaneously such as selatogrel[42] may offer an alternative way of achieving rapid $P2Y_{12}$
287 inhibition even in the pre-hospital ambulance setting. Finally, it is worth noting that the

absorption of oral antiplatelet agents can be improved by the administration of crushed ticagrelor or prasugrel through a nasogastric tube[26,43], or using orodispersible ticagrelor[44]. The PERSEUS (Platelet Inhibition After Pre-hospital Ticagrelor Using Fentanyl Compared to Morphine in Patients With ST-segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention) randomised trial (NCT02531165) will investigate the pharmacokinetics and pharmacodynamics of pre-hospital ticagrelor in patients with STEMI receiving either fentanyl or morphine. Co-administration of the antiemetic metoclopramide with morphine was recently shown to enhance ticagrelor absorption and platelet inhibition compared to morphine treatment alone in patients with unstable angina[45].

Limitations

As the studies included were observational cohort studies, there is a strong likelihood of selection bias and confounders that cannot be measured or accounted for. Exclusion of non-English studies also produces a significant limitation. The significant difference in baseline clinical characteristics between morphine and no-morphine groups in the FAST-MI study have already been discussed. Another significant risk is that patients needing morphine analgesia may be fundamentally different from those not requiring morphine. Patients with severe pain (those most likely to receive morphine) are likely to seek earlier medical attention and reperfusion may be therefore more prompt, than in patients with less severe pain or a more innocuous presentation, where diagnosis and treatment may be more delayed. It was not possible to compare the studies for pain-to-reperfusion time in the morphine and no-morphine groups, which may be a significant confounder. We cannot determine the bias possibly resulting from concomitant GPI treatment since this was not easily obtainable in all studies and would be expected to attenuate the negative impact of morphine on $P2Y_{12}$ inhibitor effect on platelet function. Furthermore, the studies differed with respect to the type

313 of $P2Y_{12}$ inhibitor used, and the dose of morphine given was not explicitly stated. These
314 variables may have been significant confounders, since the magnitude of the morphine-$P2Y_{12}$
315 inhibitor interaction may vary by type of $P2Y_{12}$ inhibitor and may be morphine dose-
316 dependent.
317
318

Conclusion

The use of morphine treatment in patients with STEMI is associated with a higher rate of re-infarction in hospital compared to patients not receiving morphine. This may be attributable to morphine-induced delay in the absorption of orally-administered $P2Y_{12}$ inhibitors and resultant delay in onset of platelet inhibition. These concerning findings indicate the need for prospective, randomised trials to assess the impact of opiates on clinical outcomes in STEMI. Until then, measures to mitigate the morphine-oral $P2Y_{12}$ inhibitor interaction should be considered.

STUDY HIGHLIGHTS

What is the current knowledge on the topic?

Pharmacodynamic studies indicate that opioids, given to relieve pain, delay the absorption of orally-administered $P2Y_{12}$ inhibitors and the onset of platelet inhibition in patients with ST-elevation myocardial infarction (STEMI). Whether such delay in platelet inhibition impacts adversely on clinical outcomes is unclear.

What question did this study address?

Does the co-administration of opioids with orally-administered $P2Y_{12}$ inhibitors in STEMI increase the risk of short-term adverse cardiac events?

What does this study add to our knowledge?

The use of morphine treatment in patients with STEMI is associated with a higher rate of re-infarction in hospital compared to patients not receiving morphine.

How might this change clinical pharmacology or translational science?

These concerning findings indicate the need for a prospective, randomised trial to assess the impact of opioids on clinical outcomes in STEMI. Until then, measures to mitigate the morphine-oral $P2Y_{12}$ inhibitor interaction should be considered through the use of intravenous $P2Y_{12}$ inhibition.

AUTHOR CONTRIBUTIONS

Y.X.G, N.S. and D.A.G. wrote the manuscript; M.F, J.K., J.M.S, M.S and D.A.G. designed the research; Y.X.G and N.S. performed the search; Y.X.G, M.F, J.M.S and D.A.G. analysed the data.

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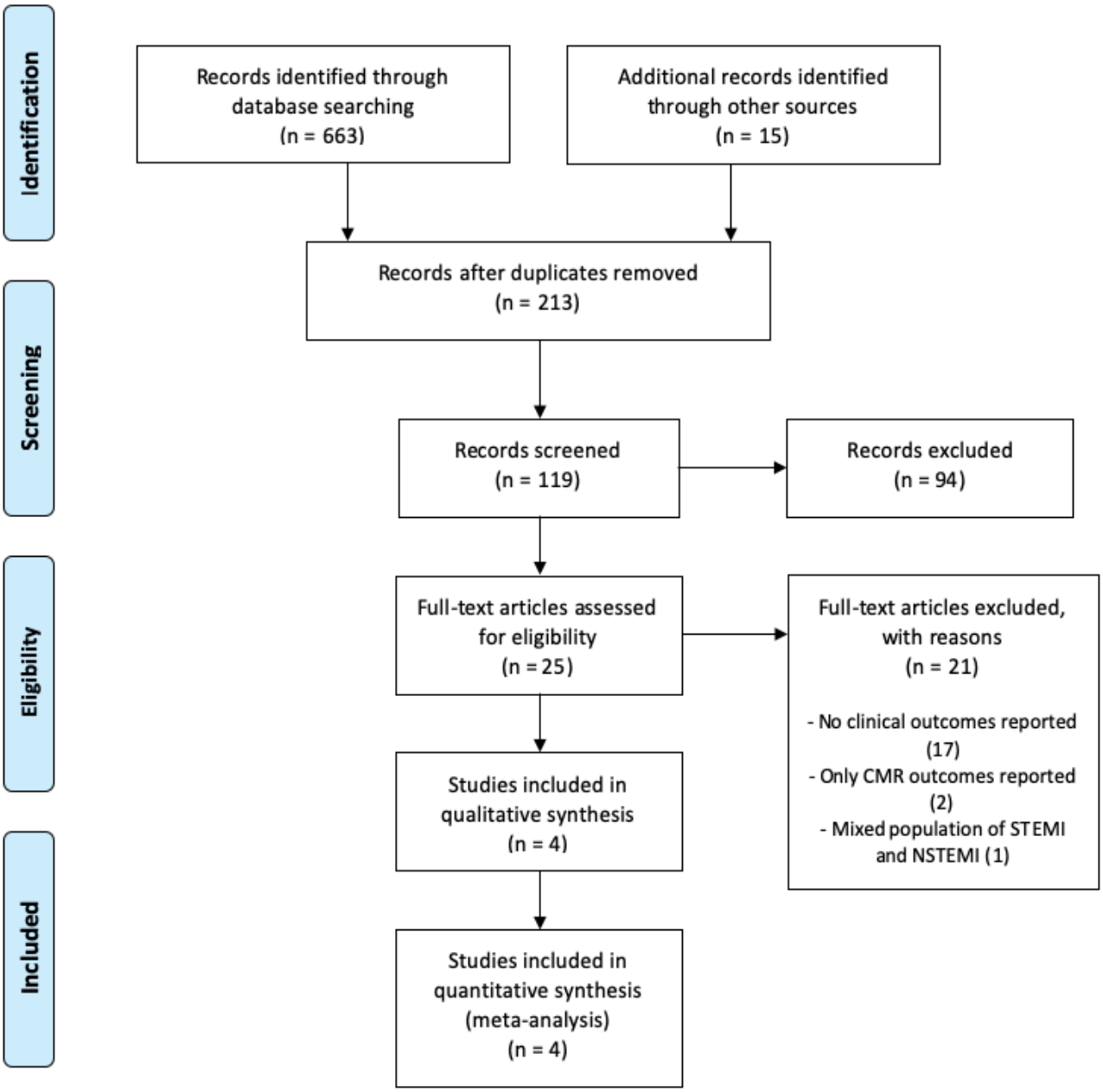
List of figures

530 Figure 1. **PRISMA flow chart**

531



532 Figure 2. **Forest plot comparing in-hospital outcomes**

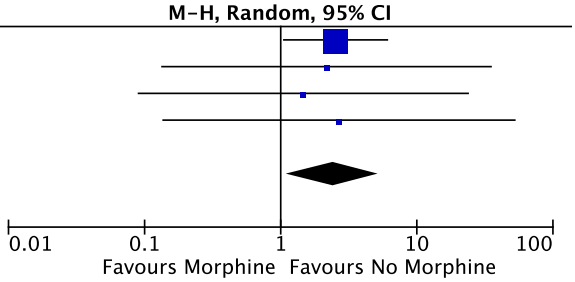
533

Reinfarction

534

Study or Subgroup	Morphine Events	Morphine Total	No Morphine Events	No Morphine Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
FAST-MI 2010	8	453	14	1985	77.9%	2.53 [1.06, 6.07]	2010
Parodi et al.	1	95	1	205	7.7%	2.17 [0.13, 35.07]	2015
Bellandi et al.	1	74	1	108	7.7%	1.47 [0.09, 23.81]	2016
Farag et al	3	218	0	82	6.7%	2.68 [0.14, 52.45]	2017
Total (95% CI)		**840**		**2380**	**100.0%**	**2.41 [1.11, 5.21]**	
Total events	13		16				

Heterogeneity: Tau² = 0.00; Chi² = 0.14, df = 3 (P = 0.99); I² = 0%
Test for overall effect: Z = 2.23 (P = 0.03)

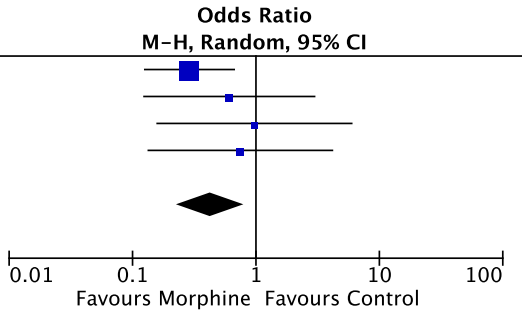


535

Death

Study or Subgroup	Morphine Events	Morphine Total	No Morphine Events	No Morphine Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
FAST-MI 2010	6	453	88	1985	58.1%	0.29 [0.13, 0.67]	2010
Parodi et al.	2	95	7	205	15.9%	0.61 [0.12, 2.98]	2015
Bellandi et al.	2	74	3	108	12.3%	0.97 [0.16, 5.97]	2016
Farag et al	4	218	2	82	13.7%	0.75 [0.13, 4.16]	2017
Total (95% CI)		**840**		**2380**	**100.0%**	**0.43 [0.23, 0.81]**	
Total events	14		100				

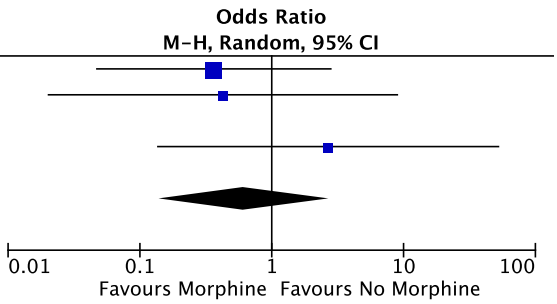
Heterogeneity: Tau² = 0.00; Chi² = 2.31, df = 3 (P = 0.51); I² = 0%
Test for overall effect: Z = 2.60 (P = 0.009)



Stroke

Study or Subgroup	Morphine Events	Morphine Total	No Morphine Events	No Morphine Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
FAST-MI 2010	1	453	12	1985	52.0%	0.36 [0.05, 2.80]	2010
Parodi et al.	0	95	2	205	23.4%	0.43 [0.02, 8.96]	2015
Bellandi et al.	0	74	0	108		Not estimable	2016
Farag et al	3	218	0	82	24.6%	2.68 [0.14, 52.45]	2017
Total (95% CI)		**840**		**2380**	**100.0%**	**0.62 [0.14, 2.69]**	
Total events	4		14				

Heterogeneity: Tau² = 0.00; Chi² = 1.25, df = 2 (P = 0.54); I² = 0%
Test for overall effect: Z = 0.64 (P = 0.52)



536 Figure 3. **Summary key message**

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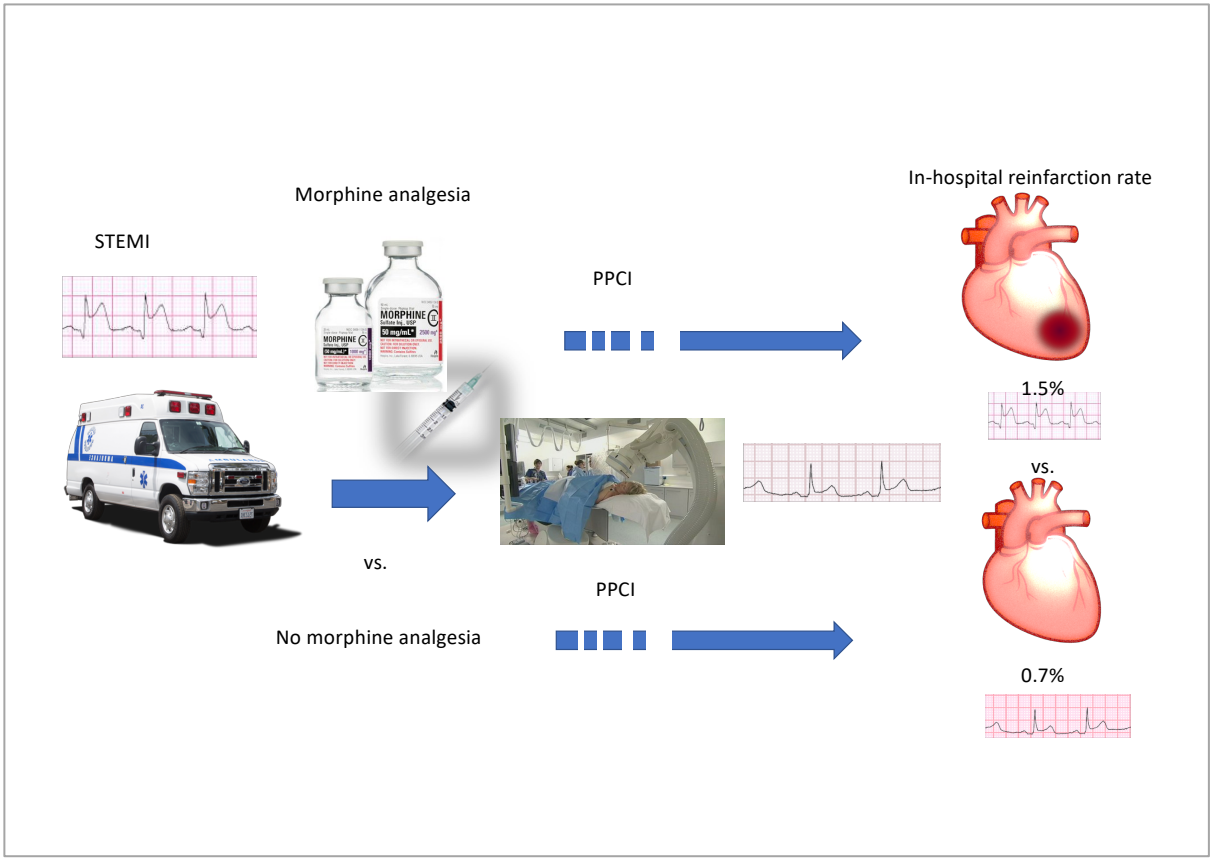

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List of Tables

563 Table 1. **Characteristics of included STEMI studies**
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565

Study	Year	Design	Study centres	P2Y12 inhibitors used	Reperfusion strategy	Follow up duration	Outcomes of interest reported	Total STEMI patients
FAST-MI 2010	2010	Retrospective cohort study	Multi-centre	Clopidogrel Prasugrel	PPCI	In-hospital 1 year	Death Recurrent MI Stroke	2438
Parodi et al.	2015	Prospective cohort study	Multi-centre	Prasugrel Ticagrelor	PPCI	In-hospital	Death Reinfarction Stroke	300
Bellandi et al.	2016	Observational study	Multi-centre	Prasugrel Ticagrelor	PPCI	In-hospital	Death Reinfarction Stroke	182
Farag et al.	2017	Observational study	Single centre	Clopidogrel Ticagrelor	PPCI	In-hospital 30-day	Death Reinfarction Stroke	300

566 Table 2. **Baseline clinical characteristics of patients in included studies.**

567 Data expressed as number N (percentage %) of patients
568 *p<0.05 for difference between morphine and no morphine groups for given clinical characteristic
569 DM = Diabetes mellitus, HTN = Hypertension, MI = Myocardial infarction, PCI = Percutaneous coronary intervention, CABG = Coronary
570 artery bypass grafting
571

Study	**Age** Mean (SD)	**Female** N (%)	**DM** N (%)	**HTN** N (%)	**Smoker** N (%)	**Dyslipidaemia** N (%)	**Previous MI** N (%)	**Previous PCI** N (%)	**Previous CABG** N (%)
FAST-MI 2010									
Morphine	59.3 (13.9)*	86 (19)*	56 (12)*	175 (39)*	239 (53)*	178 (39)	50 (11)	53 (12)	21 (5)
No morphine	64.2 (14.6)	533 (27)	333 (17)	986 (50)	762 (38)	807 (41)	210 (11)	190 (10)	100 (5)
Parodi et al.									
Morphine	62 (13)	25 (27)	14 (15)	46 (48)	54 (57)	29 (31)	8 (8)	7 (7)	1 (1)
No morphine	61.1 (12.6)	43 (21)	23 (11)	111 (54)	108 (53)	77 (38)	14 (7)	11 (5)	2 (1)
Bellandi et al.									
Morphine	64 (13)	20 (27)	12 (16)	41 (55)	36 (49)	18 (24)	6 (8)	4 (6)	1 (1)
No morphine	64 (13)	26 (24)	25 (23)	65 (60)	49 (45)	32 (30)	9 (8)	9 (8)	1 (1)
Farag et al.									
Morphine	64 (13)	48 (22)	34 (16)	107 (49)	75 (34)	NA	24 (11)	25 (12)	3 (1)
No morphine	63 (12)	16 (20)	18 (22)	44 (54)	23 (29)		10 (12)	8 (10)	1 (1)

572