

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

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

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

19  
20 Key words: Morphine, reinfarction, STEMI, PPCI

21  
22 Corresponding author: Prof. Diana A Gorog, [d.gorog@imperial.ac.uk](mailto:d.gorog@imperial.ac.uk)  
23 National Heart & Lung Institute,  
24 Imperial College, Dovehouse Street,  
25 London SW3 6LY, United Kingdom  
26 Tel: +44 (0) 207 034 8934  
27

28  
29 **Conflict of Interest**

30 All authors declared no competing interests for this work.

31  
32 **Funding**

33 This article was not funded by any external sources.  
34

35 **Abstract**

36 Opiates are the traditional analgesics used for pain relief in patients with ST-elevation  
37 myocardial infarction (STEMI). Pharmacodynamic studies indicate that opiates delay the  
38 absorption of orally-administered P2Y<sub>12</sub> inhibitors and the onset of platelet inhibition.

39 Whether the negative effect of opiates on platelet inhibition impacts on clinical outcomes is  
40 unclear.

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

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

52 Patients undergoing PPCI who are pre-treated with morphine have a higher rate of re-  
53 infarction than patients not receiving morphine. This may be attributable to opiate-related  
54 delay in P2Y<sub>12</sub> inhibitor absorption and resultant delay in onset of platelet inhibition. These  
55 concerning findings indicate the need for prospective, randomised trials to assess the impact  
56 of opiates on clinical outcomes in STEMI.

57

58 *Abstract word count: 231 words*

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

## 69 **Introduction**

70

71 Morphine is the traditional analgesic mainstay for patients presenting with ST-elevation  
72 myocardial infarction (STEMI) and has been used in this setting for >100 years. Whilst  
73 opiates continue to be used to relieve the symptoms of chest pain, without evidence base, the  
74 other treatment strategies for STEMI have significantly evolved, through the use of primary  
75 percutaneous coronary intervention (PPCI) to establish epicardial flow and the need to  
76 minimise re-occlusion and stent thrombosis through the use of potent P2Y<sub>12</sub> inhibitors<sup>1</sup>.  
77 However, concerns have arisen in the last few years about the potential adverse effects of  
78 morphine in the setting of acute coronary syndrome (ACS), where it may delay the  
79 absorption of orally-administered P2Y<sub>12</sub> inhibitors and potentially result in delayed onset of  
80 P2Y<sub>12</sub> inhibitor-mediated platelet inhibition<sup>2,3</sup>.

81 The CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress  
82 Adverse Outcomes with Early Implementation of the American College of  
83 Cardiology/American Heart Association Guidelines) registry<sup>4</sup> was one of the first to report a  
84 possible negative effect of morphine administration in ACS. Subsequently, a number of  
85 studies evaluating the effect of morphine on clinical outcomes in patients with ACS have  
86 shown that morphine delays and attenuates the effect of oral P2Y<sub>12</sub> inhibitors<sup>5-7</sup>. The Platelet  
87 Aggregation with Ticagrelor Inhibition and Fentanyl (PACIFY) randomized trial showed that  
88 fentanyl, in the same way as morphine, delayed the absorption and action of oral ticagrelor  
89 loading in patients undergoing percutaneous coronary intervention (PCI), evidenced by  
90 reduced platelet inhibition, indicating that this is likely to be a class effect<sup>8</sup>. Based on these  
91 and other studies, the European Society of Cardiology (ESC)<sup>1</sup> and the American College of  
92 Cardiology Foundation/American Heart Association (ACCF/AHA)<sup>9</sup> have downgraded the  
93 level of evidence for the use of intravenous opioids in the setting of STEMI from level I to  
94 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<sup>10-12</sup>. The  
99 potential adverse impact of opiates on P2Y<sub>12</sub> 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.

105  
106  
107  
108

## 107 **Methods**

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<sup>13</sup>.

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-

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

127 The PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses)<sup>14</sup>  
128 guidelines for reporting systematic reviews and meta-analyses.

129

### 130 *Inclusion and exclusion criteria*

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

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

139

### 140 *Endpoints*

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

143

### 144 *Data Extraction*

145 Data were independently extracted from relevant published articles by two authors (Y.G. and  
146 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<sup>15</sup>.

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<sup>16</sup>. 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<sup>14</sup>.

162

163 **Results**

164

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

172 Four publications (5 studies) involving a total of 4946 patients with STEMI were identified  
173 as suitable for inclusion<sup>6,11,12,33</sup> (Figure 1). One publication, the French Registry of Acute ST-  
174 elevation and non-ST- elevation Myocardial Infarction (FAST-MI) programme<sup>11</sup>, reported  
175 data from 2010 and additional data from another observational study in 2005 within the  
176 paper. However, as there were few patients within the FAST-MI 2005 cohort who were  
177 treated with PCI (35.1% of entire cohort) and since 27.4% of those patients were treated with  
178 pre-hospital fibrinolysis, we felt the cohort of FAST-MI 2005 was significantly different to  
179 the cohorts of other studies in the analysis, where PPCI was the default strategy. In particular,  
180 the pre-hospital fibrinolysis would have likely negated any adverse effect of the morphine-  
181 P2Y<sub>12</sub> inhibitor interaction. Hence, we excluded FAST-MI 2005 from the main analysis.

182 The characteristics of the studies included in the analysis are detailed in Table 1 and  
183 definition of outcomes in the studies in Supplementary Table 1. Baseline clinical  
184 characteristics of patients in both treatment arms are shown in Table 2. In the FAST-MI 2010  
185 study, patients treated with morphine were significantly lower risk, being younger, with  
186 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.

207

208

209

210

211

212 **Discussion**

213

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

216 Prior publications show that there is an important pharmacodynamic interaction between

217 opiates and P2Y<sub>12</sub> inhibitors. Opiates, such as morphine and fentanyl, appear to delay the

218 onset of effect and reduce the maximal platelet inhibition achieved by oral P2Y<sub>12</sub> inhibitors

219 (clopidogrel, ticagrelor, prasugrel) in patients with ACS,<sup>5,24,33,34</sup> by reducing gastrointestinal

220 absorption<sup>35</sup>. In an elegant cross-over trial in patients with stable coronary artery disease,

221 morphine, compared to saline, significantly delayed prasugrel absorption and delayed the

222 onset of adequate platelet inhibition<sup>22</sup>. However, the clinical impact of this pharmacodynamic

223 interaction is less well understood, and there have been no prospective randomised trials

224 comparing clinical outcomes of patients with STEMI treated with morphine and without

225 morphine. Our study provides evidence that the morphine-P2Y<sub>12</sub> inhibitor interaction may

226 have more than just pharmacodynamic impact, and may have important adverse clinical

227 consequences.

228 Reinfarction within the first few days after PPCI for STEMI is usually attributable to stent

229 thrombosis. The aetiology of this relates to patient-related, lesion-related, procedural, and

230 post-procedural factors<sup>36</sup>. These factors predispose to stent thrombosis generally by triggering

231 a recurrent or persistent prothrombotic state attributable to exposure of blood to stent struts,

232 and/or polymer material, leading to activation of the extrinsic pathway of the coagulation

233 cascade, persistent slow coronary flow and low shear stress leading to activation of the

234 intrinsic pathway or inadequate pharmacological suppression of platelet activation.

235 The role of suboptimal platelet inhibition as a contributor to early stent thrombosis is well

236 recognised. A large-scale meta-analysis of 221,066 patients with 4,276 episodes of stent

237 thrombosis, reported early DAPT discontinuation amongst the 3 most consistently reported

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

243 In addition to the studies reported here, the potential adverse clinical impact of a morphine-  
244 P2Y<sub>12</sub> inhibitor interaction is supported by a study in 276 STEMI patients treated with PPCI,  
245 in which morphine use was an independent predictor of larger infarct size on cardiac MRI<sup>18</sup>  
246 and an observational study of nearly 1000 patients with anterior STEMI, showing a non-  
247 significant trend towards a higher rate of recurrent MI in patients treated with, compared to  
248 those not treated with, morphine (3.8% vs. 1.7%, p=0.08)<sup>27</sup>.

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

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

263 published ATLANTIC-Morphine study<sup>41</sup>. 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<sup>41</sup>. 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<sub>12</sub> 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<sub>12</sub> 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<sub>12</sub> inhibition  
284 through the use of the intravenous P2Y<sub>12</sub> inhibition cangrelor<sup>2,34</sup> or through the use of  
285 additional parenteral antithrombotic agents such as GPI<sup>2,31,34</sup>. Newer P2Y<sub>12</sub> inhibitors given  
286 subcutaneously such as selatogrel<sup>42</sup> may offer an alternative way of achieving rapid P2Y<sub>12</sub>  
287 inhibition even in the pre-hospital ambulance setting. Finally, it is worth noting that the

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

297

### 298 *Limitations*

299 As the studies included were observational cohort studies, there is a strong likelihood of  
300 selection bias and confounders that cannot be measured or accounted for. Exclusion of non-  
301 English studies also produces a significant limitation. The significant difference in baseline  
302 clinical characteristics between morphine and no-morphine groups in the FAST-MI study  
303 have already been discussed. Another significant risk is that patients needing morphine  
304 analgesia may be fundamentally different from those not requiring morphine. Patients with  
305 severe pain (those most likely to receive morphine) are likely to seek earlier medical attention  
306 and reperfusion may be therefore more prompt, than in patients with less severe pain or a  
307 more innocuous presentation, where diagnosis and treatment may be more delayed. It was not  
308 possible to compare the studies for pain-to-reperfusion time in the morphine and no-  
309 morphine groups, which may be a significant confounder. We cannot determine the bias  
310 possibly resulting from concomitant GPI treatment since this was not easily obtainable in all  
311 studies and would be expected to attenuate the negative impact of morphine on P2Y<sub>12</sub>  
312 inhibitor effect on platelet function. Furthermore, the studies differed with respect to the type

313 of P2Y<sub>12</sub> 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<sub>12</sub>  
315 inhibitor interaction may vary by type of P2Y<sub>12</sub> inhibitor and may be morphine dose-  
316 dependent.

317

318

319 **Conclusion**

320  
321 The use of morphine treatment in patients with STEMI is associated with a higher rate of re-  
322 infarction in hospital compared to patients not receiving morphine. This may be attributable  
323 to morphine-induced delay in the absorption of orally-administered P2Y<sub>12</sub> inhibitors and  
324 resultant delay in onset of platelet inhibition. These concerning findings indicate the need for  
325 prospective, randomised trials to assess the impact of opiates on clinical outcomes in STEMI.  
326 Until then, measures to mitigate the morphine-oral P2Y<sub>12</sub> inhibitor interaction should be  
327 considered.

328

329

330

331

332

333

334

335

336

337

338

339

340

341

342 **STUDY HIGHLIGHTS**

343 *What is the current knowledge on the topic?*

344 Pharmacodynamic studies indicate that opioids, given to relieve pain, delay the absorption of  
345 orally-administered P2Y<sub>12</sub> inhibitors and the onset of platelet inhibition in patients with ST-  
346 elevation myocardial infarction (STEMI). Whether such delay in platelet inhibition impacts  
347 adversely on clinical outcomes is unclear.

348 *What question did this study address?*

349 Does the co-administration of opioids with orally-administered P2Y<sub>12</sub> inhibitors in STEMI  
350 increase the risk of short-term adverse cardiac events?

351 *What does this study add to our knowledge?*

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

354 *How might this change clinical pharmacology or translational science?*

355 These concerning findings indicate the need for a prospective, randomised trial to assess the  
356 impact of opioids on clinical outcomes in STEMI. Until then, measures to mitigate the  
357 morphine-oral P2Y<sub>12</sub> inhibitor interaction should be considered through the use of  
358 intravenous P2Y<sub>12</sub> inhibition.

359

360

361 **AUTHOR CONTRIBUTIONS**

362 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  
363 research; Y.X.G and N.S. performed the search; Y.X.G, M.F, J.M.S and D.A.G. analysed the  
364 data.



365 **References**

366

- 367 1. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of  
368 acute myocardial infarction in patients presenting with ST-segment elevation. *Eur*  
369 *Heart J* 2018; 39: 119–177. doi: 10.1093/eurheartj/ehx393
- 370 2. Giannopoulos G, Deftereos S, Kolokathis F, et al. P2Y12 Receptor Antagonists and  
371 Morphine: A Dangerous Liaison? *Circ Cardiovasc Interv*; 9. Epub ahead of print  
372 September 2016. DOI: 0.1161/circinterventions.116.004229.
- 373 3. Farag M, Spinthakis N, Srinivasan M, et al. Should STEMI Patients Receive Opiate  
374 Analgesia? The Morphine Paradox. *Curr Vasc Pharmacol* 2018; 16: 477–483. doi:  
375 10.2174/1570161116666180117145704.
- 376 4. Meine TJ, Roe MT, Chen AY, et al. Association of intravenous morphine use and  
377 outcomes in acute coronary syndromes: Results from the CRUSADE Quality  
378 Improvement Initiative. *Am Heart J* 2005; 149: 1043–1049. DOI:  
379 10.1016/j.ahj.2005.02.010
- 380 5. Silvain J, Storey RF, Cayla G, et al. P2Y12 receptor inhibition and effect of morphine  
381 in patients undergoing primary PCI for ST-segment elevation myocardial infarction.  
382 *Thromb Haemost* 2016; 116: 369–378. doi: 10.1160/TH15-12-0944
- 383 6. Bellandi B, Zocchi C, Xanthopoulou I, et al. Morphine use and myocardial reperfusion  
384 in patients with acute myocardial infarction treated with primary PCI. *Int J Cardiol*  
385 2016; 221: 567–571. doi: 10.1016/j.ijcard.2016.06.204
- 386 7. Kubica J, Adamski P, Ostrowska M, et al. Morphine delays and attenuates ticagrelor  
387 exposure and action in patients with myocardial infarction: the randomized, double-  
388 blind, placebo-controlled IMPRESSION trial. *Eur Heart J* 2016; 37: 245–252. doi:  
389 10.1093/eurheartj/ehv547
- 390 8. Ibrahim K, Shah R, Goli R, et al. Fentanyl Delays the Platelet Inhibition Effects of

- 391 Oral Ticagrelor: Full Report of the PACIFY Randomized Clinical Trial. *Thromb*  
392 *Haemost* 2018; 118: 1409–1418. doi: 10.1055/s-0038-1666862
- 393 9. O’Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA Guideline for the  
394 Management of ST-Elevation Myocardial Infarction. *Circulation* 2013; 127: e362-425.  
395 doi: 10.1161/CIR.0b013e3182742cf6
- 396 10. McCarthy CP, Bhambhani V, Pomerantsev E, et al. In-hospital outcomes in invasively  
397 managed acute myocardial infarction patients who receive morphine. *J Interv Cardiol*  
398 2018; 31: 150–158. doi: 10.1111/joic.12464.
- 399 11. Puymirat E, Lamhaut L, Bonnet N, et al. Correlates of pre-hospital morphine use in  
400 ST-elevation myocardial infarction patients and its association with in-hospital  
401 outcomes and long-term mortality: the FAST-MI (French Registry of Acute ST-  
402 elevation and non-ST-elevation Myocardial Infarction) pr. *Eur Heart J* 2016; 37:  
403 1063–1071. doi: 10.1093/eurheartj/ehv567
- 404 12. Farag M, Spinthakis N, Srinivasan M, et al. Morphine Analgesia Pre-PPCI Is  
405 Associated with Prothrombotic State, Reduced Spontaneous Reperfusion and Greater  
406 Infarct Size. *Thromb Haemost* 2018; 118: 601–612. doi: 10.1055/s-0038-1629896.
- 407 13. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in  
408 epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in  
409 Epidemiology (MOOSE) group. *JAMA* 2000; 283: 2008–12. DOI:  
410 10.1001/jama.283.15.2008
- 411 14. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews  
412 and meta-analyses: the PRISMA Statement. *Open Med* 2009; 3: e123-30.
- 413 15. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; 7:  
414 177–88. DOI: 10.1016/0197-2456(86)90046-2
- 415 16. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias

- 416 in non-randomised studies of interventions. *BMJ* 2016; 355: i4919. doi:  
417 <https://doi.org/10.1136/bmj.i4919>
- 418 17. Gwag H Bin, Park TK, Song Y Bin, et al. Morphine Does Not Affect Myocardial  
419 Salvage in ST-Segment Elevation Myocardial Infarction. *PLoS One* 2017; 12:  
420 e0170115. doi: 10.1371/journal.pone.0170115
- 421 18. de Waha S, Eitel I, Desch S, et al. Intravenous morphine administration and  
422 reperfusion success in ST-elevation myocardial infarction: insights from cardiac  
423 magnetic resonance imaging. *Clin Res Cardiol* 2015; 104: 727–734. doi:  
424 10.1007/s00392-015-0835-2
- 425 19. Eshraghi A, Tayyebi M, Sajjadi SS, et al. Morphine Post-Conditioning Effect on QT  
426 Dispersion in Patients Undergoing Primary Percutaneous Coronary Intervention on  
427 Anterior Descending Cardiac Artery: A Cohort Study. *Electron physician* 2017; 9:  
428 3468–3474. doi: 10.19082/3468
- 429 20. Xanthopoulou I, Davlouros P, Tsigkas G, et al. Factors Affecting Platelet Reactivity 2  
430 Hours After P2Y<sub>12</sub> Receptor Antagonist Loading in Primary Percutaneous Coronary  
431 Intervention for ST-Elevation Myocardial Infarction – Impact of Pain-to-Loading  
432 Time. *Circ J* 2016; 80: 442–449. doi: 10.1253/circj.CJ-15-0495
- 433 21. Flierl U, Zauner F, Sieweke J-T, et al. Efficacy of prasugrel administration  
434 immediately after percutaneous coronary intervention in ST-elevation myocardial  
435 infarction. *Thromb Haemost* 2017; 117: 99–104. doi: 10.1160/TH16-07-0569
- 436 22. Thomas M, Morton A, Hossain R, et al. Morphine delays the onset of action of  
437 prasugrel in patients with prior history of ST-elevation myocardial infarction. *Thromb*  
438 *Haemost* 2016; 116: 96–102. doi: 10.1160/TH16-02-0102
- 439 23. Parodi G, Bellandi B, Valenti R, et al. Comparison of double (360 mg) ticagrelor  
440 loading dose with standard (60 mg) prasugrel loading dose in ST-elevation myocardial

- 441 infarction patients: The Rapid Activity of Platelet Inhibitor Drugs (RAPID) primary  
442 PCI 2 study. *Am Heart J* 2014; 167: 909–914. doi: 10.1016/j.ahj.2014.03.011
- 443 24. Johnson TW, Mumford AD, Scott LJ, et al. A Study of Platelet Inhibition, Using a  
444 ‘Point of Care’ Platelet Function Test, following Primary Percutaneous Coronary  
445 Intervention for ST-Elevation Myocardial Infarction [PINPOINT-PPCI]. *PLoS One*  
446 2015; 10: e0144984. doi: 10.1371/journal.pone.0144984
- 447 25. Parodi G, Valenti R, Bellandi B, et al. Comparison of Prasugrel and Ticagrelor  
448 Loading Doses in ST-Segment Elevation Myocardial Infarction Patients. *J Am Coll*  
449 *Cardiol* 2013; 61: 1601–1606. doi: 10.1016/j.jacc.2013.01.024
- 450 26. Rollini F, Franchi F, Hu J, et al. Crushed Prasugrel Tablets in Patients With STEMI  
451 Undergoing Primary Percutaneous Coronary Intervention. *J Am Coll Cardiol* 2016; 67:  
452 1994–2004. doi: 10.1016/j.jacc.2016.02.045.
- 453 27. Bonin M, Mewton N, Roubille F, et al. Effect and Safety of Morphine Use in Acute  
454 Anterior ST-Segment Elevation Myocardial Infarction. *J Am Heart Assoc*; 7. Epub  
455 ahead of print 20 February 2018. DOI: 10.1161/JAHA.117.006833.
- 456 28. Franchi F, Rollini F, Cho JR, et al. Impact of Escalating Loading Dose Regimens of  
457 Ticagrelor in Patients With ST-Segment Elevation Myocardial Infarction Undergoing  
458 Primary Percutaneous Coronary Intervention. *JACC Cardiovasc Interv* 2015; 8: 1457–  
459 1467. doi: 10.1016/j.jcin.2015.02.030.
- 460 29. Iakobishvili Z, Porter A, Battler A, et al. Effect of Narcotic Treatment on Outcomes of  
461 Acute Coronary Syndromes. *Am J Cardiol* 2010; 105: 912–916. doi:  
462 10.1016/j.amjcard.2009
- 463 30. Zeymer U, Mochmann H-C, Mark B, et al. Double-Blind, Randomized, Prospective  
464 Comparison of Loading Doses of 600 mg Clopidogrel Versus 60 mg Prasugrel in  
465 Patients With Acute ST-Segment Elevation Myocardial Infarction Scheduled for

- 466 Primary Percutaneous Intervention. *JACC Cardiovasc Interv* 2015; 8: 147–154. doi:  
467 10.1016/j.jcin.2014.09.007.
- 468 31. Siller-Matula JM, Specht S, Kubica J, et al. Abciximab as a bridging strategy to  
469 overcome morphine-prasugrel interaction in STEMI patients. *Br J Clin Pharmacol*  
470 2016; 82: 1343–1350. doi: 10.1111/bcp.13053
- 471 32. Everts B, Karlson B, Abdon N-J, et al. A comparison of metoprolol and morphine in  
472 the treatment of chest pain in patients with suspected acute myocardial infarction - the  
473 MEMO study. *J Intern Med* 1999; 245: 133–141. DOI: 10.1046/j.1365-  
474 2796.1999.00415.x
- 475 33. Parodi G, Bellandi B, Xanthopoulou I, et al. Morphine Is Associated With a Delayed  
476 Activity of Oral Antiplatelet Agents in Patients With ST-Elevation Acute Myocardial  
477 Infarction Undergoing Primary Percutaneous Coronary Intervention. *Circ Cardiovasc*  
478 *Interv*; 8. Epub ahead of print January 2015. DOI:  
479 10.1161/CIRCINTERVENTIONS.114.001593.
- 480 34. Kubica J, Kubica A, Jilma B, et al. Impact of morphine on antiplatelet effects of oral  
481 P2Y12 receptor inhibitors. *Int J Cardiol* 2016; 215: 201–208. doi:  
482 10.1016/j.ijcard.2016.04.077.
- 483 35. Nimmo WS, Heading RC, Wilson J, et al. Inhibition of gastric emptying and drug  
484 absorption by narcotic analgesics. *Br J Clin Pharmacol* 1975; 2: 509–13. DOI:  
485 10.1111/j.1365-2125.1975.tb00568.x
- 486 36. Claessen BE, Henriques JPS, Jaffer FA, et al. Stent Thrombosis. *JACC Cardiovasc*  
487 *Interv* 2014; 7: 1081–1092. doi: 10.1016/j.jcin.2014.05.016.
- 488 37. D’Ascenzo F, Bollati M, Clementi F, et al. Incidence and predictors of coronary stent  
489 thrombosis: Evidence from an international collaborative meta-analysis including 30  
490 studies, 221,066 patients, and 4276 thromboses. *Int J Cardiol* 2013; 167: 575–584.

- 491 doi: 10.1016/j.ijcard.2012.01.080.
- 492 38. Velders MA, Abtan J, Angiolillo DJ, et al. Safety and efficacy of ticagrelor and  
493 clopidogrel in primary percutaneous coronary intervention. *Heart* 2016; 102: 617–625.  
494 doi: 10.1136/heartjnl-2015-308963.
- 495 39. Stone GW, Witzenbichler B, Guagliumi G, et al. Bivalirudin during Primary PCI in  
496 Acute Myocardial Infarction. *N Engl J Med* 2008; 358: 2218–2230. doi:  
497 10.1056/NEJMoa0708191.
- 498 40. Dangas G, Aymong ED, Mehran R, et al. Predictors of and outcomes of early  
499 thrombosis following balloon angioplasty versus primary stenting in acute myocardial  
500 infarction and usefulness of abciximab (the CADILLAC trial). *Am J Cardiol* 2004; 94:  
501 983–988. DOI: 10.1016/j.amjcard.2004.06.050
- 502 41. Lapostolle F, Van't Hof AW, Hamm CW, et al. Morphine and Ticagrelor Interaction  
503 in Primary Percutaneous Coronary Intervention in ST-Segment Elevation Myocardial  
504 Infarction: ATLANTIC-Morphine. *Am J Cardiovasc Drugs* 2019; 19: 173–183. doi:  
505 10.1007/s40256-018-0305-0.
- 506 42. Juif P, Boehler M, Dobrow M, et al. Clinical Pharmacology of the Reversible and  
507 Potent P2Y<sub>12</sub> Receptor Antagonist ACT-246475 After Single Subcutaneous  
508 Administration in Healthy Male Subjects. *J Clin Pharmacol* 2019; 59: 123–130. doi:  
509 10.1002/jcph.1296.
- 510 43. Parodi G, Xanthopoulou I, Bellandi B, et al. Ticagrelor Crushed Tablets  
511 Administration in STEMI Patients. *J Am Coll Cardiol* 2015; 65: 511–512. doi:  
512 10.1016/j.jacc.2014
- 513 44. European Medicines Agency. Brilique,  
514 <https://www.ema.europa.eu/en/medicines/human/EPAR/brilique> (accessed 2 July  
515 2019).

516 45. Sikora J, Niezgoda P, Barańska M, et al. METoclopramide Administration as a  
517 Strategy to Overcome MORPHine-ticagrelOr Interaction in PatientS with Unstable  
518 Angina PectorIS-The METAMORPHOSIS Trial. *Thromb Haemost* 2018; 118: 2126–  
519 2133. doi: 10.1055/s-0038-1675605.

520

521

522

523 **List of figures**

524

525 Figure 1. PRISMA flow-chart

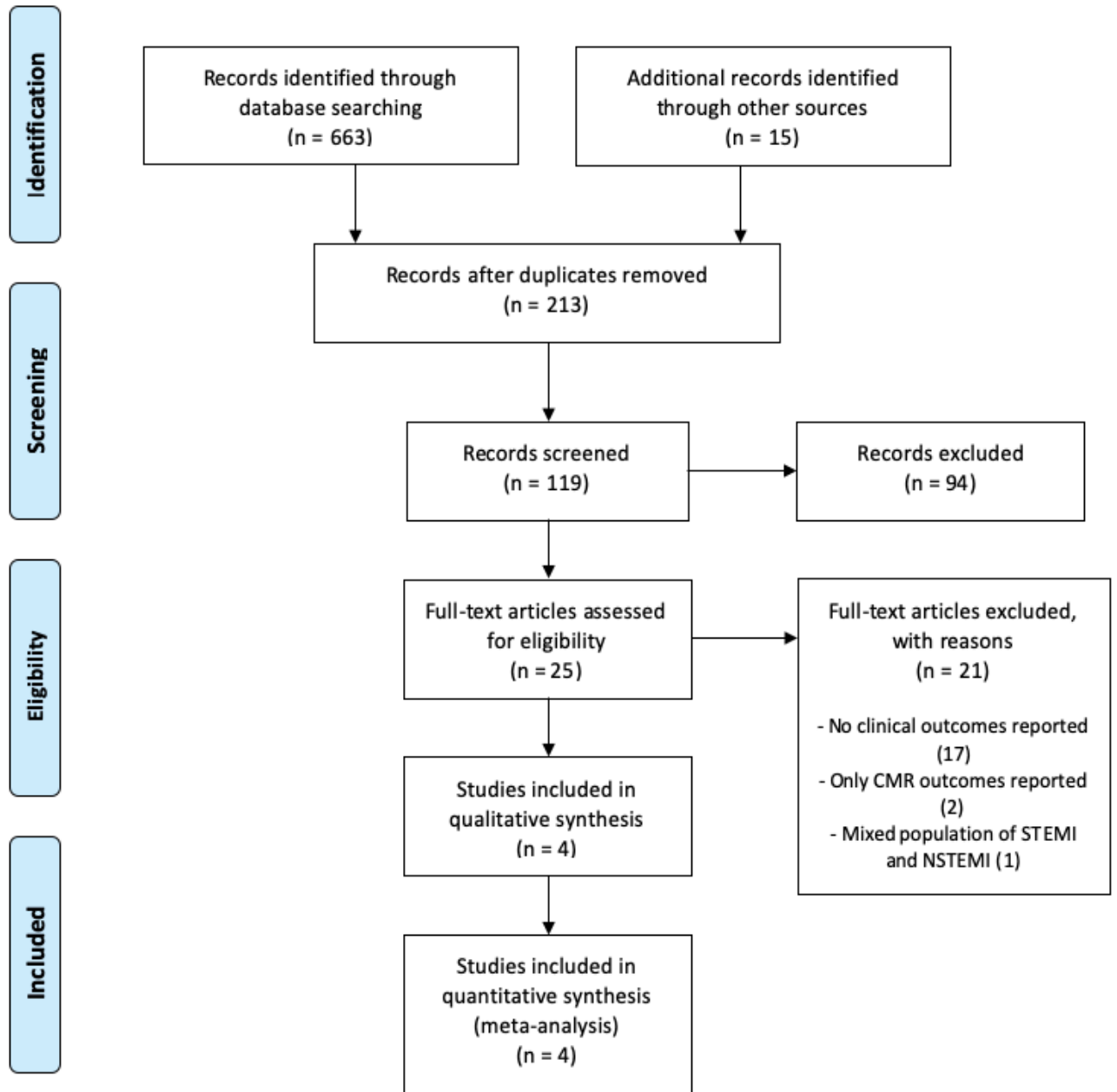
526 Figure 2. Forest plot comparing in-hospital outcomes

527 Figure 3. Summary key message

528

529



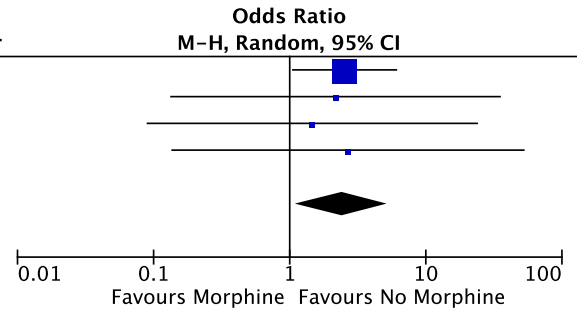


522

**Reinfarction**

534

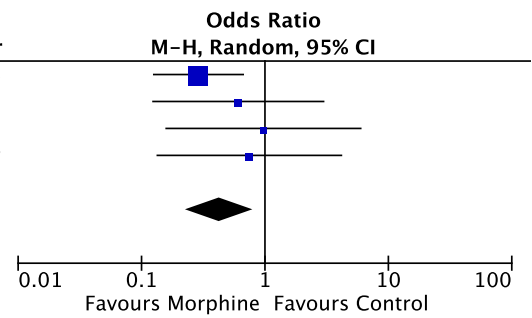
Study or Subgroup	Morphine		No Morphine		Weight	Odds Ratio M-H, Random, 95% CI	Year
	Events	Total	Events	Total			
FAST-MI 2010	8	453	14	1985	77.9%	2.53 [1.06, 6.07]	2010
Parodi et al.	1	95	1	205	7.7%	2.17 [0.13, 35.07]	2015
Bellandi et al.	1	74	1	108	7.7%	1.47 [0.09, 23.81]	2016
Farag et al	3	218	0	82	6.7%	2.68 [0.14, 52.45]	2017
<b>Total (95% CI)</b>		<b>840</b>		<b>2380</b>	<b>100.0%</b>	<b>2.41 [1.11, 5.21]</b>	
Total events	13		16				
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.14, df = 3 (P = 0.99); I <sup>2</sup> = 0%							
Test for overall effect: Z = 2.23 (P = 0.03)							



535

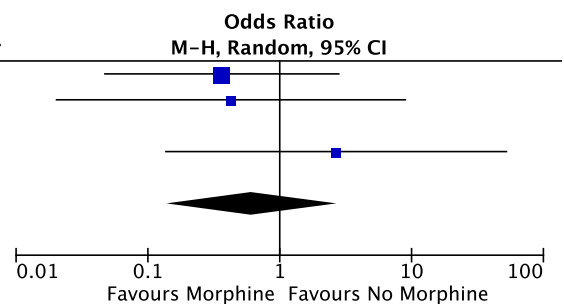
**Death**

Study or Subgroup	Morphine		No Morphine		Weight	Odds Ratio M-H, Random, 95% CI	Year
	Events	Total	Events	Total			
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
<b>Total (95% CI)</b>		<b>840</b>		<b>2380</b>	<b>100.0%</b>	<b>0.43 [0.23, 0.81]</b>	
Total events	14		100				
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 2.31, df = 3 (P = 0.51); I <sup>2</sup> = 0%							
Test for overall effect: Z = 2.60 (P = 0.009)							



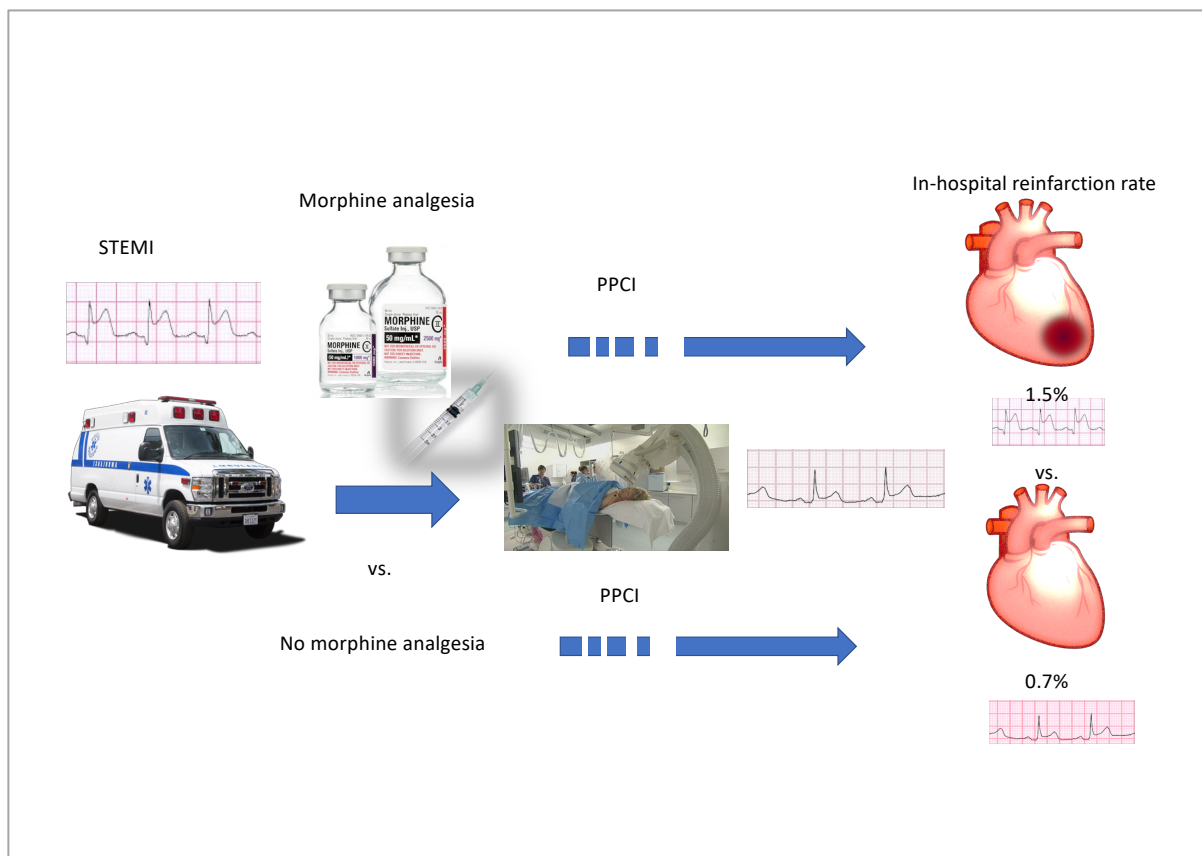
**Stroke**

Study or Subgroup	Morphine		No Morphine		Weight	Odds Ratio M-H, Random, 95% CI	Year
	Events	Total	Events	Total			
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
<b>Total (95% CI)</b>		<b>840</b>		<b>2380</b>	<b>100.0%</b>	<b>0.62 [0.14, 2.69]</b>	
Total events	4		14				
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 1.25, df = 2 (P = 0.54); I <sup>2</sup> = 0%							
Test for overall effect: Z = 0.64 (P = 0.52)							



536 Figure 3. Summary key message

537



538

539

540 **List of Tables**

541

542

543 Table 1. Characteristics of included STEMI studies

544

545 Table 2. Baseline characteristics of included studies

546

547

548

549

550

551

552

553

554

555

556

557

558

559

560

561

562

563 Table 1. Characteristics of included STEMI studies  
564

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

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

572