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Association of peri-procedural intravenous morphine use on clinical outcomes in ST-elevation myocardial infarction (STEMI) treated by primary percutaneous coronary intervention: systematic review and meta-analysis

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ABSTRACT

Objectives: To conduct a systematic review and meta-analysis of studies examining the impact of peri-procedural intravenous morphine on clinical outcomes in patients undergoing primary percutaneous coronary intervention (PCI) for ST-elevation myocardial infarction (STEMI).

Background: Morphine analgesia may reduce the absorption of co-prescribed P2Y12 antagonists attenuating platelet inhibition. The impact of periprocedural intravenous morphine on clinical outcomes in patients undergoing PCI for STEMI is not well defined.

Methods: Analysis of the electronic databases of MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, Web of Science and ClinicalTrials.gov for association of peri-PCI intravenous morphine use with in-hospital or 30-day myocardial infarction (MI) (primary outcome) and in-hospital or 30-day mortality.

Results: 11 studies were included for systematic review. One study was a randomised controlled trial, 10 were observational studies. Five studies including 3748 patients were included in meta-analysis of in-hospital or 30-day MI. Within this group, patients were treated concurrently with ticagrelor (n=2239), clopidogrel (n=1256) and prasugrel (n=253). There was no significant association of in-hospital or 30-day MI with intravenous morphine

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(odds ratio 1.88; 95% confidence interval (CI) 0.87-4.09; I^2 0%). Across seven studies and 5800 patients, no increased risk of mortality at the same composite time endpoint was evident (odds ratio 0.70; 95% CI 0.40-1.23; I^2 19%).

Conclusions: Peri-procedural intravenous morphine administration was not associated with adverse short-term clinical outcomes in patients undergoing primary PCI for STEMI. Further randomized trial data are needed to evaluate the pharmacologic interaction between morphine and P2Y12 antagonists with clinical outcomes.

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INTRODUCTION

Intravenous morphine analgesia is currently recommended to relieve symptoms associated with acute myocardial infarction (AMI) and to reduce sympathetic tone which leads to increased cardiac workload.[1] However, due to the lack of clinical trials demonstrating benefit on clinical outcomes with morphine, in addition to observational data suggesting that morphine might be associated with increase mortality and major adverse cardiovascular events (MACE) in non-ST elevation acute coronary syndromes (NSTEACS),[2] the level of evidence for morphine analgesia across international guidelines is low.[1, 3]

In healthy volunteers randomised to intravenous morphine or placebo while co-prescribed a P2Y12 inhibitor, recent data have demonstrated a potential pharmacokinetic interaction between morphine and clopidogrel,[4] ticagrelor[5] and prasugrel.[6] By decreasing or slowing plasma levels of antiplatelet agents and their active metabolites, it is suggested that the onset of inhibition of platelet aggregation is delayed. In patients with ST-elevation myocardial infarction (STEMI) receiving ticagrelor randomised to intravenous morphine or placebo, the IMPRESSION trial also found that morphine attenuated ticagrelor action.[7] Further prospective observational data in STEMI patients have reported higher residual platelet reactivity in patients receiving ticagrelor or prasugrel while co-prescribed intravenous morphine.[8] It has been postulated that the pharmacokinetic interaction between morphine and P2Y12 inhibitors may translate to failure of optimal anti-platelet

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treatment in AMI and subsequently lead to poor clinical outcomes in morphine treated patients.[4-8]

In spite of the above data suggesting an adverse effect of morphine and P2Y12 inhibitors absorption and reduced anti-platelet effect, recent studies have yielded conflicting results as to whether the proposed drug-drug interaction between intravenous morphine and P2Y12 inhibitors impacts clinical outcomes.[9-11] To address this, we performed a systematic review and meta-analysis to examine the impact of intravenous morphine analgesia on reinfarction and mortality in patients with STEMI undergoing primary percutaneous coronary intervention (PCI).

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METHODS

This systematic review and meta-analysis was reported in accordance with the set of items outlined by Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement.[12] The written protocol has been registered on PROSPERO: International prospective register of systematic reviews (ID number CRD42019117374).[13]

Search strategy

Systematic searches of the electronic databases MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, Web of Science and ClinicalTrials.gov were conducted, including articles from database inception until 20 November 2018. Electronic search strings included medical subject headings and search terms pertaining to the intervention morphine in combination with myocardial infarction of any subtype to ensure broad capture of potentially relevant studies. A limit for the inclusion of human participants was established though no further limits with relation to year of publication or language of publication were implemented. Editorial articles, letters, non-primary studies and grey literature were also screened for potentially relevant studies that may have been otherwise missed.

Study selection

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Original, peer reviewed articles with human participants over the age of 18 were included. Studies were included if they reported exposure to pre-hospital or peri-procedural intravenous morphine in patients with STEMI who underwent primary PCI. Studies that could not be retrieved in full text form, and conference abstracts, were included. Randomised controlled trials and observational studies were included, however, case reports and case series were excluded. Authors of studies containing potentially relevant information were contacted to retrieve additional data for analysis.

All studies identified by the search strategy were imported into Covidence[14] and duplicates deleted. Two review authors (RB and DL) independently completed title and abstract screen of all identified studies. The same two review authors then independently assessed the full texts of all studies potentially meeting inclusion criteria. A third review author (SN) mediated any discordance in assessments.

Data extraction

Two review authors (RB and DL) extracted data from included studies using a standardised, pre-piloted data extraction tool based on the minimum requirements recommended in the Cochrane Handbook for Systematic Reviews.[15] This process was completed independently,

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with any discrepancy on comparison mediated by discussion and re-evaluation of the included study.

Risk of bias analysis

Risk of bias was assessed independently by two review authors (RB and DL). Discordance in assessment was resolved by a third author (JB). Methodological quality of randomised controlled trials was assessed using the Cochrane Tool for Assessing Risk of Bias.[16] The Newcastle-Ottawa Scale[17] was used to assess the quality of observational studies and post-hoc analyses of randomised controlled trials.

Statistical analysis

Studies that reported on myocardial infarction (MI), mortality, or MACE at a composite time end-point of either in-hospital or at 30-days follow up underwent meta-analysis. The primary outcome was in-hospital or 30-day MI. Measures of association were reported, including odds ratios (OR), relative risks (RR) and hazard ratios (HR) were extracted from each study with a 95% confidence interval (CI) and p-value. Unadjusted odds ratios were calculated using the Peto method where adjusted estimates were not available.[18] Data returned by randomised controlled trials was pooled separately to observational or longitudinal data. Review Manager 5.3[19] software was used to generate summary effects

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estimates and to calculate the variance of the overall effect. Forest plots were generated within the same software in each dataset using the generic inverse variance method as to include adjusted measures of association reported by the observational dataset. Random effects modelling was used in view of methodological heterogeneity across included studies. The I^2 statistic was used to estimate the degree to which measures of effect varied.

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RESULTS

Search results

The systematic search yielded 2522 unique articles, of which 2439 were excluded on title and abstract screen based on relevance to the inclusion criteria. The remaining 82 studies underwent full text screen, of which a further 71 articles were excluded. The most common reasons for exclusion were reporting of outcomes irrelevant to the present study (n=24), incorrect patient populations (including those with NSTEMI) (n=23), and interventions other than primary PCI, or administration of another opiate or by alternative route (n=15). A summary of the screening process with detailed reasons for exclusion is presented using the PRISMA flow diagram in Figure 1.[12] In total, 11 studies were included for systematic review.[7-11, 20-25]

Qualitative synthesis

The 11 included studies consisted of a single randomised controlled trial,[7] two post-hoc analyses of randomised controlled trials,[11, 24] and eight cohort studies.[8-10, 20-23, 25] In total, the included studies accounted for 10476 patients, with an average age of 62.3 years, 23.1% (n=2420) of whom were female. Ten studies published clinical outcome data for all-cause mortality,[7-11, 20, 22-25] eight published data on MI or reinfarction[7-9, 11, 20, 22-24] and a further

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eight on MACE as a combined endpoint.[7, 9-11, 21-24] A detailed summary of study characteristics is included in Table 1.

Length of follow up also varied within the observational dataset. Outcome data was collected by studies over a duration ranging from in-hospital stay to over one year. Five studies presented clinical outcome data for hospital stay only, the median of which ranged from 3.0 to 5.9 days.[7, 8, 20, 24, 25] Two studies presented clinical outcomes at 30 days,[10, 22] and four studies presented data at one year or over.[9, 11, 21, 23] Two studies presented hazard ratios for clinical outcomes at one year.[9, 11] In post-hoc analysis of the CIRCUS clinical trial, Bonin *et al*[11] reported a hazard ratio at one year of 1.25; 95% CI 0.96-1.62, p=0.10 for MACE with periprocedural intravenous morphine. Puymirat *et al*[9] demonstrated that within the FAST-MI 2010 cohort, one-year survival according to pre-hospital morphine was associated with a hazard ratio of 0.69, 95% CI 0.35-1.37, p=0.29. Both results were adjusted for multiple baseline characteristics.

The single clinical trial, the IMPRESSION trial, was a single-centre double-blind study that randomised 70 patients undergoing primary PCI to receive either morphine 5mg or placebo intravenously followed by a 180mg loading dose of ticagrelor.[7] Primary endpoints were pharmacokinetic; however, clinical outcome data was also collected. There was no in-hospital death or MI in either arm which precluded from estimating a summary effect for these clinical outcomes, however, the intervention arm recorded one stent thrombosis

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which was included as a MACE. Importantly, only 64.5% of patients were STEMI patients as this trial also included a small population of patients with NSTEMI. This presented an additional limitation in pooling the results of this trial.

The observational dataset included two post-hoc analyses of clinical trials: the CIRCUS randomised controlled trial, in which patients undergoing primary PCI for STEMI were randomised to cyclosporine;[11] the ATLANTIC trial, in which patients undergoing primary PCI for STEMI were randomised to receive pre- versus in-hospital ticagrelor.[24] Both studies reported on mortality, MACE and MI, with post-hoc analysis of the CIRCUS trial reporting outcomes at one year and the post-hoc analysis of the ATLANTIC trial reporting outcomes in hospital.

Of the eight cohort studies, Puymirat *et al*[9] included data from the FAST-MI 2005 and FAST-MI 2010 cohorts, of which only data from the FAST-MI 2010 was included as only 35.1% of the FAST-MI 2005 cohort underwent primary PCI. Across the observational dataset, specific concurrent P2Y12 inhibitors included in studies were: ticagrelor (n=6), clopidogrel (n=5), and prasugrel (n=3). Almost all patients were treated with a P2Y12 inhibitor, with the exceptions being the Bonin *et al* post-hoc analysis (>90% in both arms discharged on dual antiplatelet therapy),[11] the McCarthy *et al* cohort study (>90% of patients received a P2Y12 inhibitor),[25] and the Iakobishvili *et al* cohort study (in which the percentage was unclear).[10] All cohort studies utilised registry data or medical records in ascertaining outcome and exposure, with

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the exception of one study that employed structured interview and telephone questionnaire linked to hospital records.[21]

The definition of MACE varied between observational studies. Broadly, a combination of cardiovascular death, recurrent MI, cardiogenic shock, stroke, coronary revascularisation following index procedure and stent thrombosis characterised this outcome, but this was not homogenous. Variations in definition of MACE is detailed in Table 1.

Risk of bias analysis

The 11 studies included were generally of good methodological quality.

A summary of risk of bias assessment for the 11 studies included in meta-analysis are presented in Supplementary 2. The single randomised controlled trial utilised random allocation software and randomisation kits and was thus judged at low risk of selection bias.[7] Four observational studies that were deemed of low risk of bias in comparability as they adjusted for a broad range of baseline characteristics, including age, gender, previous ACS, infarct size, T2DM, smoking, hypercholesterolaemia, door to balloon time and haemodynamic parameters.[9-11, 25] Six studies did not perform multivariate adjustment of their findings and were therefore deemed at high risk of bias in this domain.[8, 20-24] Selection of observational cohorts was well conducted across all studies. The four observational

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studies that assessed clinical outcomes within hospital-stay only lost a point in length of follow up on the Newcastle-Ottawa quality assessment scale.[8, 20, 24, 25]

A funnel plot for each of the included clinical outcomes was generated to assess publication bias across observational studies, with asymmetry testing demonstrating low risk (Supplementary 3). In addition to this, methodological efforts were made to limit potential publication bias, such as including conference abstracts as part of the search strategy.

Meta-analysis of in-hospital or 30-day myocardial infarction

Seven observational studies reported on recurrent MI with intravenous morphine use in peri-procedural primary PCI.[8, 9, 11, 20, 22-24] Two studies were excluded from meta-analysis as they presented clinical outcomes at one year and did not publish in-hospital or 30-day data.[11, 23] The Puymirat *et al*[9] FAST-MI 2010 study presented crude data as well as data with patients only on peri-procedural thienopyridines, of which only the latter dataset was included. 3748 participants from the remaining five studies were pooled in meta-analysis.[8, 9, 20, 22, 24] Data adjusted for multiple variables or statistical imbalance was included preferentially to crude measures of association. Unadjusted measures of effect were included alongside adjusted data with the use of generic inverse variance modelling. None of the five cohorts included for meta-analysis demonstrated a statistically significant association. Random-effects meta-analysis generated an overall odds ratio of in-hospital or

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30-day MI with morphine in STEMI patients undergoing primary PCI of 1.88 (95% CI 0.87-4.09, p=0.90, I^2 0%) (Figure 3).

Meta-analysis of in-hospital or 30-day all-cause mortality

Nine observational studies reported on mortality with periprocedural morphine.[8-11, 20, 22-25] Data pooled from seven studies that reported mortality in-hospital or at 30-days included 5800 participants.[8-10, 20, 22, 24, 25] Meta-analysis of these seven studies observed no increased risk of mortality with intravenous morphine at the composite time endpoint of in-hospital or 30-days, OR 0.70 (95% CI 0.40-1.23, p=0.28, I^2=19%) (Figure 3).

Meta-analysis of in-hospital or 30-day major adverse cardiovascular events

The single randomised controlled trial of 70 participants randomised to 5mg of intravenous morphine or placebo prior to primary PCI recorded one stent thrombosis in the experimental group which was counted as a MACE (Figure 5).[7] Seven of the 10 observational studies included in this systematic review reported on MACEs,[9-11, 21-24] with four reporting MACE in-hospital or at 30 days.[9, 10, 22, 24] These four studies included 4031 participants that underwent PCI for STEMI. None of the individual studies demonstrated a statistically significant association. Pooled results from these studies demonstrated no significant

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association between peri-procedural morphine use and MACE – OR 1.04 (95% CI 0.64-1.69, p=0.14, I^2=45%) (Figure 4).

Subgroup and sensitivity analyses

Limiting meta-analysis to observational studies at lowest risk of bias (Newcastle Ottawa scale score = 9) was consistent with primary analyses and did not produce statistically significant results in mortality or MACE subgroups (OR 0.36; 95% CI 0.15-0.83, I2 33% and OR 0.74; 95% CI 0.48-1.14, I^2 0% respectively).[9, 10] Only one study within the MI subgroup was afforded a full score of 9, thus this outcome could not undergo subgroup analysis in this domain.[9] As multiple unadjusted measures of effect were included in primary analyses, subgroup analysis of studies reporting only adjusted measures of association was conducted, which did not reach statistical significance in any domain.[9, 10, 25] The effects estimate generated by pooling three studies that published data on MI with IV morphine and ticagrelor did not reach statistical significance (OR 1.95; 95% CI 0.53-7.25, I^2 0%).[8, 20, 24] Two studies pooled that published data on MI with IV morphine and clopidogrel did not reach statistical significance (OR 1.85; 95% CI 0.70-4.89, I^2 1%).[9, 22] Subgroups were generated based on the majority P2Y12 inhibitor used as outcome data specific to each medication was not available. Further subgroup analysis, including limiting to in-hospital follow up, is included in Supplement 4.

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DISCUSSION

The results of this systematic review of 11 studies did not show evidence of increased risk of poor clinical outcomes with intravenous morphine analgesia in patients undergoing primary PCI for STEMI. Meta-analysis of 3748 participants across five observational studies found a positive association between intravenous morphine use and in-hospital or 30-day MI, however, this result did not reach statistical significance. Meta-analysis of 5800 participants across seven observational studies found no association between intravenous morphine use and in-hospital or 30-day all-cause mortality. Pooled results from four observational studies (4031 participants) reporting composite outcome endpoints for MACE with intravenous morphine use also demonstrated no statistical association.

This is the first meta-analysis examining intravenous morphine use and clinical outcomes in patients undergoing primary PCI for STEMI. Since the early 20th century,[26, 27] morphine has been a first line agent to treat chest pain caused by MI. Since inception of the use of morphine, it has been proposed that the agent's pharmacodynamic effects, such as reduction in heart rate and blood pressure, may also decrease myocardial oxygen demand, all important beneficial physiological effects in patients with STEMI.[28] To date, there has not been a large scale randomised clinical trial examining the benefit and safety of intravenous morphine use in patients with ACS. As a result, and in view of emerging concerns regarding

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a potential interaction between morphine and co-prescribed P2Y12 inhibitors, current major guideline recommendations for the use of morphine in ACS report a low level of evidence.[1, 3]

The CRUSADE registry reported in-hospital clinical outcomes in 57039 patients with NSTEACS across 443 hospitals in the United States from January 2001 through June 2003. 66.1% of patients underwent diagnostic catheter angiography, 36.5% proceeded to PCI, and 11.5% underwent coronary artery bypass graft surgery.[2] Within 24 hours of presentation, 17003 (29.8%) patients were treated with morphine. In morphine treated patients, an increased risk of in-hospital death (adjusted OR = 1.48, 95% CI 1.33-1.64), post-admission MI (adjusted OR 1.34, 95% CI 1.22-1.48) and cardiogenic shock (adjusted OR 1.71, 95% CI 1.53-1.91) was observed. The results of the CRUSADE study were some of the first to raise concerns regarding the use of morphine in patients with NSTEMI. Subsequently, more recent studies have reported that, in healthy subjects loaded with P2Y12 inhibitors, concomitant intravenous morphine could delay maximal inhibition of platelet aggregation; delay clopidogrel absorption and decrease plasma levels of its active metabolite;[4] delay ticagrelor absorption and decrease levels of its active metabolite (while not demonstrating diminishing antiplatelet effects);[5] and delay maximal plasma concentration of prasugrel and its active metabolite (while not demonstrating diminishing antiplatelet effects).[6] These observations and findings have been corroborated in STEMI patients as well, with morphine use found to be an independent predictor of high residual platelet reactivity in patients

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randomised to ticagrelor and prasugrel in the RAPID primary PCI study published by Parodi *et al* in 2013.[29] Morphine administration was also found to attenuate the exposure and action of ticagrelor and its active metabolite in patients with STEMI randomised to morphine or placebo in the IMPRESSION trial.[7] In 2015 an observational study suggested that, in STEMI patients, intravenous morphine may negatively impact myocardial salvage and ischemic injury as assessed by cardiac magnetic resonance imaging.[21] However, a subsequent observational study in 2017 demonstrated that intravenous morphine administration prior to PCI in STEMI patients did not negatively impact myocardial salvage following propensity score-matched analysis.[23]

In view of the presently available data, this systematic review and meta-analysis found no clear association between morphine use and adverse short-term clinical outcomes, notwithstanding any possible effect on haemodynamic, biochemical or imaging evaluation parameters.

Potential mechanisms outside drug-drug interactions

While biological factors such as gender and age have demonstrated little pharmacokinetic impact of thienopyridine absorption,[30] morphine has across multiple studies been shown to

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affect pharmacokinetics and antiplatelet effects.[4-6, 8, 22, 24] It has been proposed that morphine lowers plasma concentration of P2Y12 inhibitors and their active metabolites through reducing gastrointestinal absorption of P2Y12 inhibitors,[7] as it activates opioid receptors in the intestinal tract and myenteric plexus which in turn decreases gut motility and secretions.[31] Specific to patients with STEMI, sympathetic activation and shunting of blood to perfuse vital organs may also exacerbate poor intestinal motility and, consequently, delaying absorption of P2Y12 inhibitors further.[32] This may explain why studies examining the effect of intravenous morphine on the antiplatelet effect of ticagrelor[5] and prasugrel[6] in healthy patients, while demonstrating lower plasma concentrations of each drug with morphine, found no reduction in the antiplatelet effect, while studies in STEMI patients report positive findings.[7, 8] Supporting this hypothesis further is that the crushed form ticagrelor has been demonstrated to provide earlier platelet inhibition when compared to standard tablets.[33] Furthermore, the known side effects of intravenous morphine, which include nausea and emesis, may also contribute to poorer bioavailability of oral antiplatelet agents in this setting,[31] though the association between morphine and delayed onset of action of oral antiplatelets has been demonstrated to persist even after excluding patients with vomiting, suggesting additional mechanisms.[8]

Morphine has been shown to decrease blood pressure and heart rate, which may in turn decrease myocardial oxygen demand and thus decrease myocardial damage in STEMI.[28]

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However, morphine also depresses respiratory drive, which may contribute to poor oxygen delivery to vital organs. In some animal models, morphine has been shown to increase MI size,[34] while other studies have reported a reduction in infarct size mediated by morphine associated ischaemic preconditioning.[35] In a few randomised studies, intracoronary morphine administration in STEMI did not lead to a reduction in MI size.[36, 37] The cardioprotective properties of morphine are, therefore, contested and require further human data.

There are also other reasons that could explain the poor clinical outcomes with intravenous morphine in patients with ACS which are not directly due to its pharmacologic effect on P2Y12 inhibitors. Firstly, at least pertinent to the observational data, selection bias might account for why some patients experiencing more severe pain due to more significant underlying myocardial damage were more likely to be treated with morphine. Secondly, morphine administration might mask ongoing or redevelopment of pain and, therefore, delay myocardial reperfusion.[2]

Limitations

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Studies included in this systematic review and meta-analysis were primarily of observational study design, with the single exception being a randomised controlled trial of 70 participants which was unable to be pooled due to study design.

A methodological limitation of the present systematic review and meta-analysis stemmed from a paucity of studies that conducted multivariate analyses. Within meta-analysis of the primary outcome, in-hospital or 30-day MI, only one of five included studies adjusted effect estimates for baseline characteristics.[9] Studies reporting unadjusted measures of effect did exclude patients with premorbid P2Y12 inhibitor use, cerebrovascular disease, glycoprotein IIb/IIIa inhibitor use, active bleeding, vomiting following dual antiplatelet therapy loading, coagulopathy and haemodynamic compromise. Nonetheless, variables such as age, sex, diabetes status, hypertension, and PCI characteristics were not reliably controlled for, which could contribute to confounding bias. Even within studies that adjusted for relevant confounders, residual confounding by unknown factors is also likely present. A lack in reporting of procedural granularity precluded analysis based on PCI characteristics. It is difficult to establish as to whether this may be masking a harmful or protective association. Within meta-analysis of mortality at 30 days, only three of seven included studies reported adjusted effects estimates, which included age, sex, diabetes status, history of ischaemic heart disease, door to balloon time and peri-procedural haemodynamic parameters.[9, 10, 25]

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Lastly, the interaction of morphine with different P2Y12 inhibitors was not able to be assessed. In attempting to address this, studies in which most participants were treated with a particular P2Y12 inhibitor were pooled in subgroup meta-analysis, though neither the clopidogrel or ticagrelor group reached statistical significance.

Conclusion

This systematic review and meta-analysis found no clear evidence of an association between morphine use and short-term clinical outcomes in patients undergoing primary PCI for STEMI likely due to the current body of evidence being largely observational and heterogenous. Well-designed, adequately powered randomised clinical trials are required to establish the effect of morphine analgesia and contemporary P2Y12 inhibitors on clinical outcomes in STEMI. In the context of currently available data, and pending a randomised clinical trial evaluating the use of morphine at the acute stage of MI, it remains advisable to continue to use morphine as appropriate in patients with severe ischemic chest pain.

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Author (year), study design	Country (time period)	Population; age in years; % Female	Ascertainment of exposure	Antiplatelet agents	Ascertainment of outcome	Outcome	Follow Up Period	Adjustment for potential confounders
Bellandi (2016),[20] prospective cohort study.	Italy, Greece (Jan 2012 – Jan 2014)	n = 182; 64.0; 25.0.	Medical records	Ticagrelor (n=131) Prasugrel (n=51)	Medical records	In hospital: Death: 3/108 no morphine, 2/74 morphine Reinfarction 1/108 no morphine, 1/74 morphine Stroke: 0/108, 0/74	In-hospital (average length of stay 3.8 days)	Unadjusted. Exclusion criteria: previous clopidogrel use; life expectancy; previous TIA/stroke; unable to consent; warfarin therapy; IIb/IIIa inhibitor administration; active bleeding/haemodynamic instability.
Bonin (2018),[11] post-hoc analysis of RCT (CIRCUS)	Europe (Apr 2011 – Feb 2014)	n = 967, 60.0, 18.0%	CIRCUS database	Not specified. >93% in both groups discharged on DAPT.	Event validation committee (3 physicians blinded)	MACE (cardiovascular death, heart failure, cardiogenic shock, recurrent MI, unstable angina, stroke): 91/413 no morphine, 145/554 morphine MACE Adjusted HR = 1.25; 95% CI 0.96-1.62, p=0.10 All-cause death: 22/413 no morphine, 32/554 morphine Cardiovascular death: 20/413 no morphine, 29/554 morphine Heart failure (development): 70/413 no morphine, 110/554 morphine Recurrent myocardial infarction: 7/413 no morphine, 21/554 morphine Unstable angina: 8/413 no morphine, 15/554 morphine Stroke: 9/413 no morphine, 10/554 morphine	One year	Adjusted for age, ischaemic time, infarct size, initial and final thrombolysis in myocardial infarction flow, sex, smoking, hypertension, diabetes mellitus, previous myocardial infarction, Killip class. Exclusion criteria: cardiogenic shock, loss of consciousness, known hypersensitivity to cyclosporine, known kidney or liver failure, pregnancy, absence of contraception in women of child-bearing age, disorders of immunological dysfunction within 6 months.
De Waha (2015),[21] prospective cohort study	Germany (Aug 2006 – Aug 2009)	n = 276, 66.0, 27.5%	Structured interview	Clopidogrel (n=276)	Structured telephone questionnaire linked to hospital records	MACE (death, non-fatal MI): 20/153 no morphine, morphine 14/123	Median 16 months	Unadjusted. Exclusion criteria: prior fibrinolysis, cardiogenic shock, contraindications to CMR
Farag (2018),[22] prospective cohort study.	United Kingdom (Apr 2015 – June 2016)	n = 300, 64.0, 21.3%	Medical records	Clopidogrel (n=259) Ticagrelor (41)	Medical records, based on European Society of Cardiology guidelines or Bleeding Academic Research Consortium definition	No statistically significant difference in event rates In-Hospital Outcome Death: 2/82 no morphine, 4/218 morphine Re-infarction: 0/82 no morphine, 3/218 morphine Stroke: 0/82 no morphine, 3/218 morphine MACE: 2/82 no morphine, 10/218 morphine 30-day outcome: Death: 2/82 no morphine, 8/218 morphine Re-infarction: 0/82 no morphine, 6/218 morphine Stroke: 0/82 no morphine, 4/218 morphine MACE: 2/82 no morphine, 18/218 morphine	Median in-hospital stay 3.0 30 days	Unadjusted. Exclusion criteria: vomiting following DAPT loading pre-PPCI, intubation, unable to swallow, premorbid oral anticoagulation, those with known coagulation disorders, low platelet count, low haemoglobin, known active malignancy, inability to take DAPT.

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Gwag (2017),[23] retrospective cohort study.	Republic of Korea (Jan 2008 – June 2014)	n = 307, 58.5, 19.8%	SMART-AMI-CMR Registry	Clopidogrel (n=299)	SMART-AMI-CMR Registry	No significant differences in MACE-free survival in crude or propensity score-matched analysis Death: 5/209 no morphine, 2/98 morphine MACE (cardiac death, recurrent MI, ischaemic stroke, coronary revascularisation following index procedure): 26/209 no morphine, 8/98 morphine MI: 5/209 no morphine, 1/98 morphine	20.6 months morphine, 28.4 months no morphine	Unadjusted. Exclusion criteria: 12 hours or more symptom to balloon time, medical treatment without primary PCI, previous history of MI, revascularisation.
Iakobishvili (2010),[10] retrospective cohort study	Israel (Mar 2008 – May 2008)	n = 765, 59.6, 18.9%	ACSIS database	Not specified Unclear if all patients were on a P2Y12 inhibitor	ACSIS database	At 30 days: Death: 6.7% no IVN, 3.1% IVN. Adjusted OR = 0.40; 95% CI 0.14-1.14, p=0.08 MACE (death, recurrent infarction, repeat ischaemia, stent thrombosis, CVA): 16.3% no IVN, 11.1% IVN. Adjusted OR = 0.69; 95% CI 0.42-1.16, p=0.16	30 days	Adjusted for age, gender, Killip class, previous MI, previous angina, previous CCF, renal failure, PVD, previous revascularisation, hypercholesterolemia, hypertension, T2DM, heart rate, systolic blood pressure, and propensity score for intravenous narcotic use, Exclusion criteria: transfer to other hospital
Kubica (2016),[7] RCT (IMPRESSION)	Poland (Aug 2014 – June 2015)	n = 70, 61.6, 27.0%	Randomised	Ticagrelor (n=70)	Not specified	In hospital: Death: 0/35 no morphine, 0/35 morphine MI: 0/35 no morphine, 0/35 morphine Stroke: 0/35 no morphine, 0/35 morphine MACE (death, MI, stent thrombosis, CVA): 0/35 no morphine, 1/35 morphine	In-hospital (average length of stay not specified)	Exclusion criteria: unbearable chest pain, request for analgesics, prior morphine administration during the current MI, treatment with any P2Y12 receptor inhibitor within 14 days, ongoing treatment with oral anticoagulant or chronic therapy with low molecular weight heparin, active bleeding, Killip class III or IV, respiratory failure, coagulation disorders.
Lapostolle (2018),[24] post hoc analysis of RCT (ATLANTIC)	Algeria, Australia, Canada, Europe (Sep 2011 – Oct 2013)	n = 1858, 60.8, 19.8%	ATLANTIC trial database	Ticagrelor (n=1862)	ATLANTIC trial database	Within 24 hours of loading dose: Death: 6/937 no morphine, 10/921 morphine, OR 1.70; 95% CI 0.62-4.71, p=0.30 MI: 2/937 no morphine, 4/921 morphine, OR 2.04; 95% CI 0.37-11.18, p=0.41 MACE (death, MI, CVA, urgent revascularisation, definite stent thrombosis): 16/937 no morphine, 18/921 morphine, OR 1.15, 95% CI 0.58-2.26, p=0.69	24 hours	Exclusion criteria: per ATLANTIC trial. Not specified in publication.
McCarthy (2018),[25] retrospective cohort study	United States (Jan 2009 – July 2016)	n = 1287, 61.4, 25.6%	MGH Cardiac Catheterisation Database	Clopidogrel (n=909) Ticagrelor (n=290)	MGH Cardiac Catheterisation Database	Death in hospital stay: 4.18% no morphine, 7.54% morphine. Adjusted OR = 0.36; 95% CI 0.08-1.68, p=0.19 Propensity matched cohort of STEMI patients – adjusted OR death = 0.58; 95% CI 0.19-1.78, p=0.34	In-hospital (average length of stay no morphine 5.91 days, morphine 5.40 days)	Adjusted for age, sex, BMI, family history of coronary artery disease, shock at PCI, hypertension, T2DM, smoking, hypercholesterolemia, heart rate, systolic blood pressure, door to balloon time, prior CABG, CCF, CVA and renal impairment

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Parodi (2015),[8] retrospective cohort study	Italy, Greece (not specified)	n = 300, 61.4, 22.7%	Various cohort studies	Ticagrelor (n=205) Prasugrel (n=95)	Not specified	In hospital stay: Death: 7/205 no morphine, 2/95 morphine Reinfarction: 1/205 no morphine, 1/95 morphine Stroke: 2/205 no morphine, 0/95 morphine	In-hospital (average not specified	Unadjusted. Exclusion criteria: age<18, active bleeding, previous CVA, administration of antiplatelet therapy in the week prior to the event, chronic anticoagulation, known haematological disorders, life expectancy <17 year, known severe liver or renal disease, haemodynamic instability.
Puymirat (2016),[9] retrospective cohort study (two cohorts)	France (FAST-MI 2010 Oct 2010 – Nov 2010; FAST-MI 2005 Oct 2005 – Nov 2005)	FAST-MI 2010 n = 2438, 63.3, 25.4% FAST-MI 2010 (pre-hospital thienopyridines only) n = 1108, 62.1, 22.1% FAST-MI 2005 n = 1726, 65.0, 29.9%	FAST-MI 2010 and 2005 registries	FAST-MI 2010: Clopidogrel (n=1726) Prasugrel (n=195) FAST-MI 2005: Clopidogrel (n=209) Not all patients were on P2Y12 inhibitor though this was separately analysed	FAST-MI 2010 and 2005 registries	FAST-MI 2010 (in-hospital): Death: 88/1985 no morphine, 6/453 morphine. Adjusted OR = 0.48; 95% CI 0.12-1.85, p=0.29 Recurrent MI: 14/1985 no morphine, 8/453 morphine. Adjusted OR 2.94; 95% CI 1.17-7.37, p=0.02 Death or recurrent MI: 99/1985 no morphine, 14/453 morphine. Adjusted OR 1.21; 95% CI 0.59-2.50, p=0.60 FAST-MI 2010 in patients receiving pre-hospital thienopyridines adjusted (in-hospital): Mortality: OR 0.28, *p* = 0.045 Recurrent MI: OR 1.35, *p* = 0.20 Stroke: OR 0.57, *p* = 0.29 One-year survival according to pre-hospital morphine use adjusted HR = 0.69, 95% CI 0.35-1.37, p=0.29 FAST-MI 2005 (in-hospital): Death: 103/1447 no morphine, 10/279 morphine. Adjusted OR = 0.48; 95% CI 0.21-1.10, p=0.08 Recurrent MI: 23/1447 no morphine, 3/279 morphine. Adjusted OR 0.75; 95% CI 0.21-2.66, p=0.65 In hospital death or recurrent MI: 118/1447 no morphine, 12/279 morphine. Adjusted OR 0.59; 95% CI 0.29-1.23, p=0.16	One year	Exclusion criteria: iatrogenic MI, ACS diagnosis invalidated, unstable angina with no cardiac biomarker increase. Adjusted for baseline characteristics and reperfusion therapy

ACS, acute coronary syndrome; CCF, congestive heart failure; CMR, cardiac magnetic resonance; CVA, cerebrovascular attack; DAPT, dual antiplatelet therapy; HR, hazard ration; IVN, intravenous narcotics; MACE, major adverse cardiovascular event; MI, myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; RCT, randomised controlled trial; TIA, transient ischaemic attack; T2DM, type 2 diabetes mellitus;

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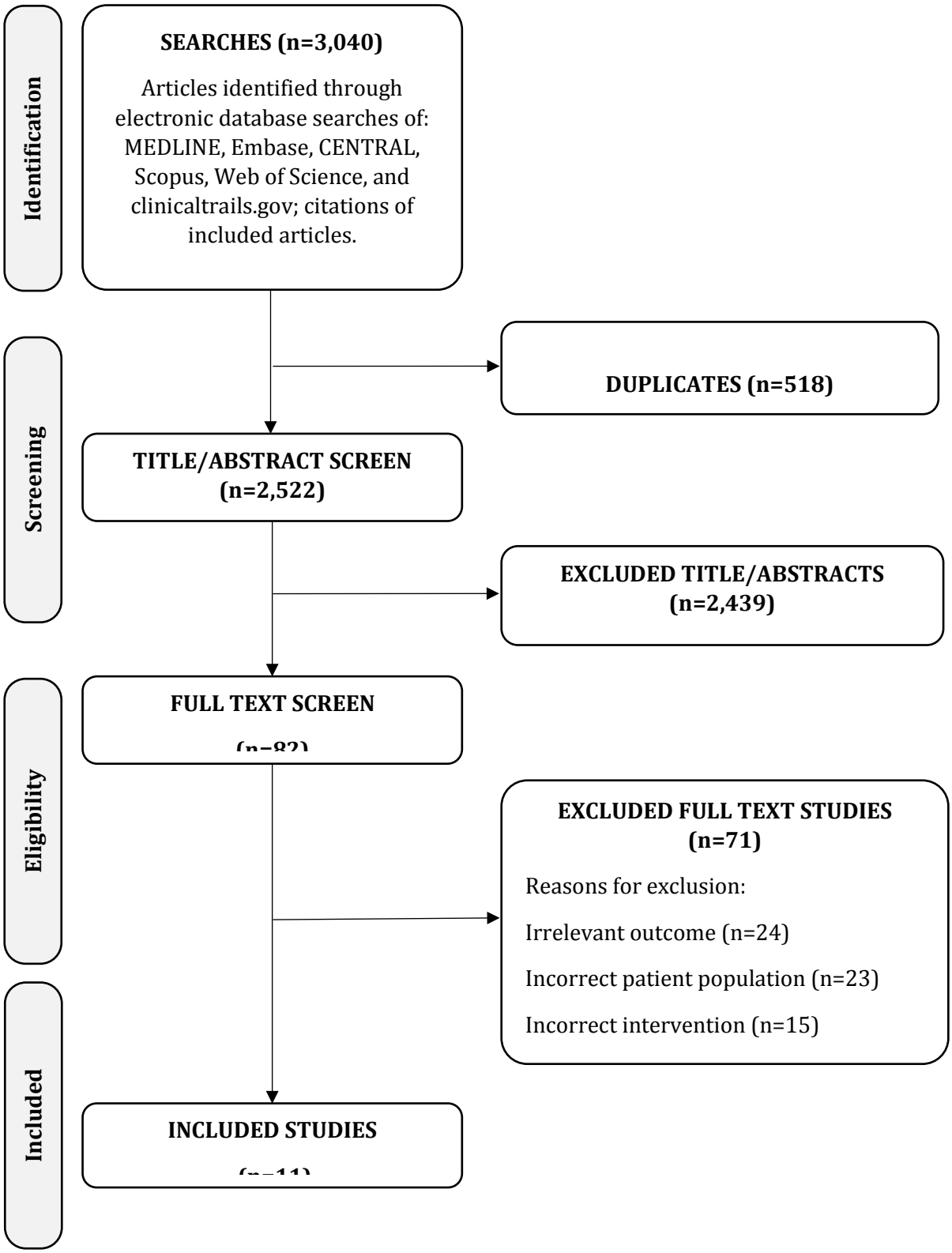

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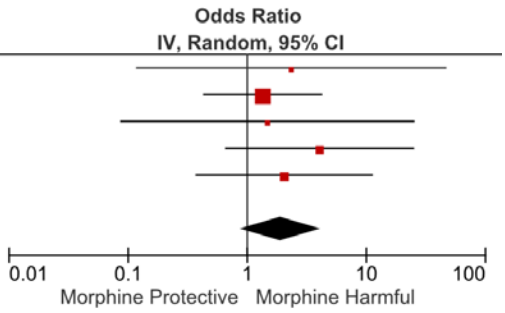
Study or Subgroup	Weight	Odds Ratio IV, Random, 95% CI
Parodi 2015	6.8%	2.34 [0.12, 46.27]
Puymirat 2016	46.6%	1.35 [0.43, 4.21]
Bellandi 2016	7.5%	1.48 [0.09, 24.99]
Farag 2018	18.3%	4.05 [0.66, 24.78]
Lapostolle 2018	20.8%	2.04 [0.37, 11.18]
Total (95% CI)	**100.0%**	**1.88 [0.87, 4.09]**

Heterogeneity: Tau² = 0.00; Chi² = 1.07, df = 4 (P = 0.90); I² = 0%
Test for overall effect: Z = 1.60 (P = 0.11)



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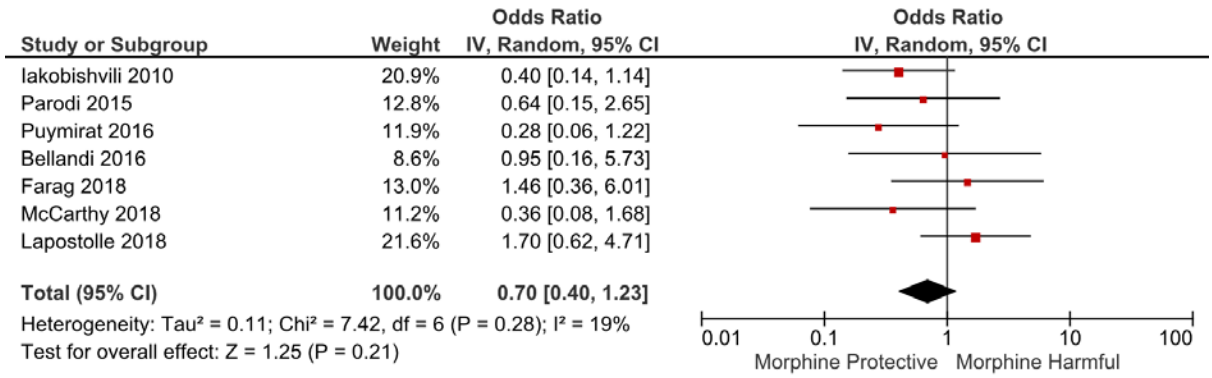

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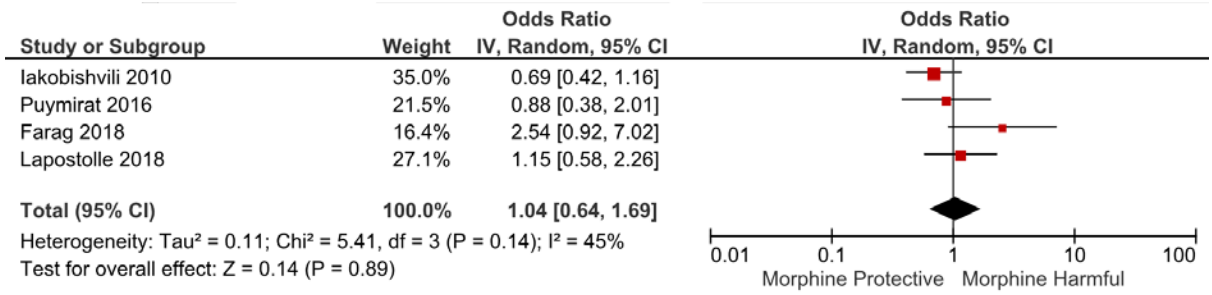

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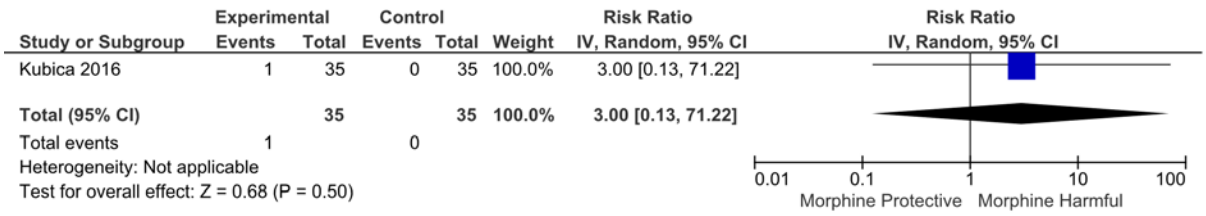

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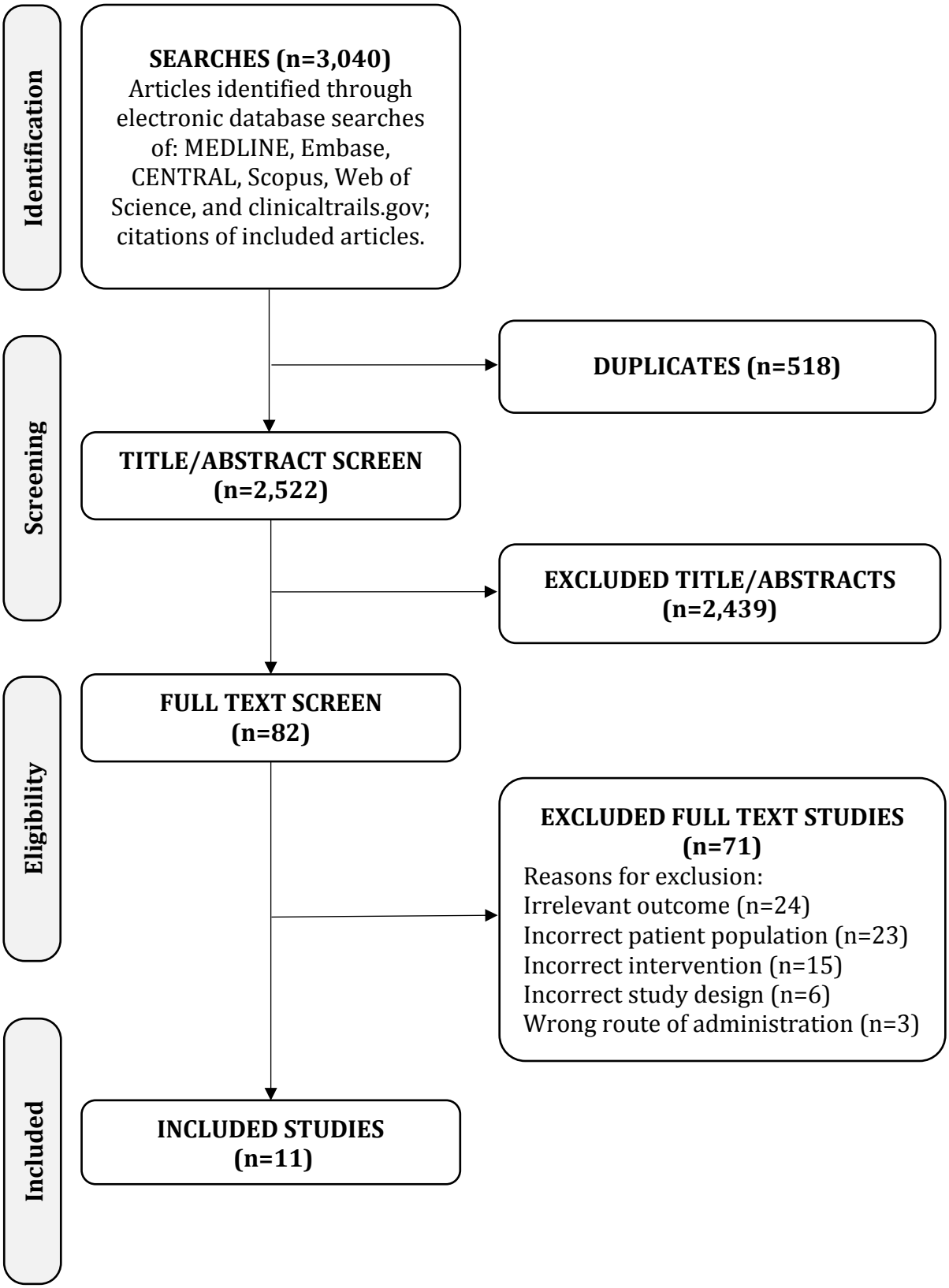

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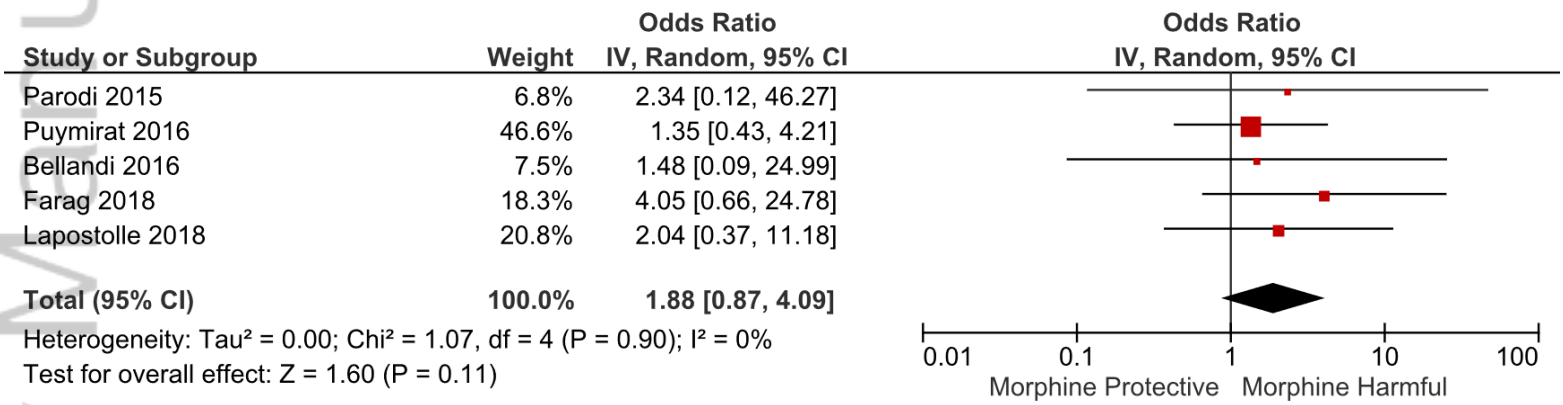

CCD_28561_Figure 2 - MI.png

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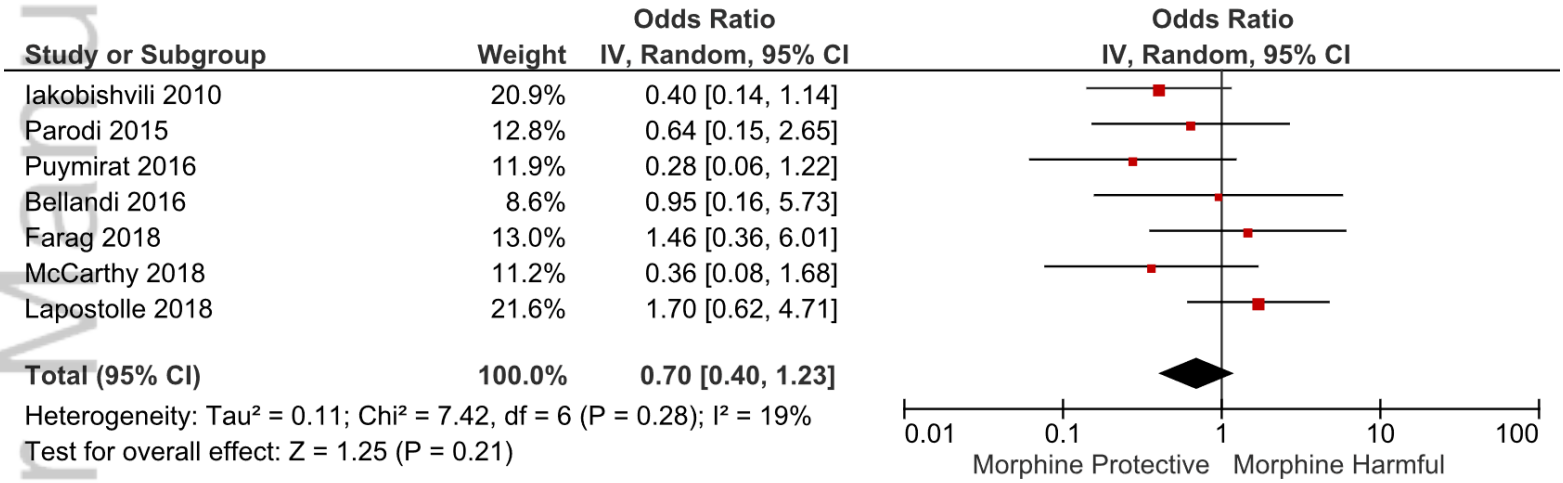

CCD_28561_Figure 3 - Mortality.png

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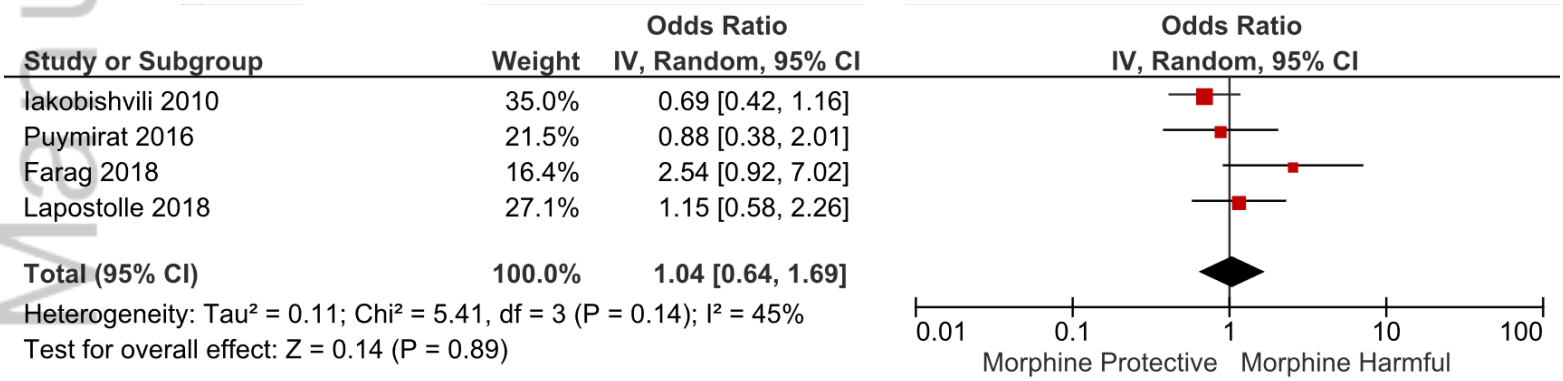

CCD_28561_Figure 4 - MACE (O).png

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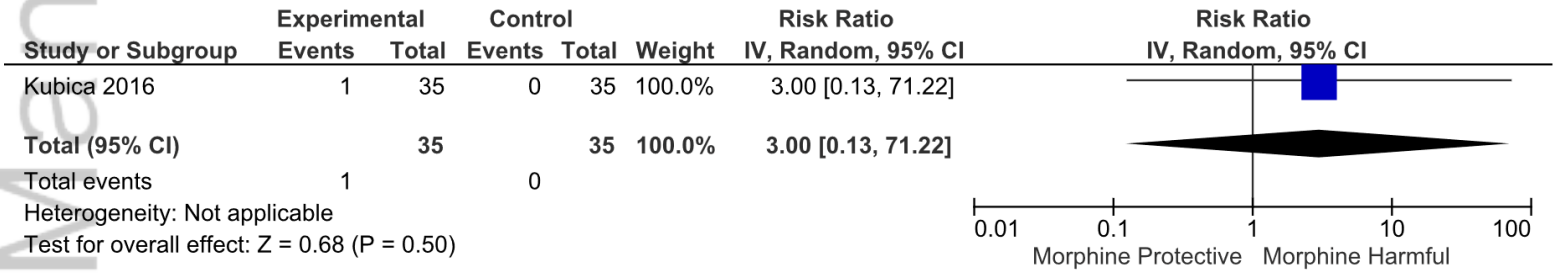

CCD_28561_Figure 5 - MACE (RCT).png

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Author (year), study design	Country (time period)	Population; age in years; % Female	Ascertainment of exposure	Antiplatelet agents	Ascertainment of outcome	Outcome	Follow Up Period	Adjustment for potential confounders
Bellandi (2016),[20] prospective cohort study.	Italy, Greece (Jan 2012 – Jan 2014)	n = 182; 64.0; 25.0.	Medical records	Ticagrelor (n=131) Prasugrel (n=51)	Medical records	In hospital: Death: 3/108 no morphine, 2/74 morphine Reinfarction 1/108 no morphine, 1/74 morphine Stroke: 0/108, 0/74	In-hospital (average length of stay 3.8 days)	Unadjusted. Exclusion criteria: previous clopidogrel use; life expectancy; previous TIA/stroke; unable to consent; warfarin therapy; IIb/IIIa inhibitor administration; active bleeding/haemodynamic instability.
Bonin (2018),[11] post-hoc analysis of RCT (CIRCUS)	Europe (Apr 2011 – Feb 2014)	n = 967, 60.0, 18.0%	CIRCUS database	Not specified. >93% in both groups discharged on DAPT.	Event validation committee (3 physicians blinded)	MACE (cardiovascular death, heart failure, cardiogenic shock, recurrent MI, unstable angina, stroke): 91/413 no morphine, 145/554 morphine MACE Adjusted HR = 1.25; 95% CI 0.96-1.62, p=0.10 All-cause death: 22/413 no morphine, 32/554 morphine Cardiovascular death: 20/413 no morphine, 29/554 morphine Heart failure (development): 70/413 no morphine, 110/554 morphine Recurrent myocardial infarction: 7/413 no morphine, 21/554 morphine Unstable angina: 8/413 no morphine, 15/554 morphine Stroke: 9/413 no morphine, 10/554 morphine	One year	Adjusted for age, ischaemic time, infarct size, initial and final thrombolysis in myocardial infarction flow, sex, smoking, hypertension, diabetes mellitus, previous myocardial infarction, Killip class. Exclusion criteria: cardiogenic shock, loss of consciousness, known hypersensitivity to cyclosporine, known kidney or liver failure, pregnancy, absence of contraception in women of child-bearing age, disorders of immunological dysfunction within 6 months.
De Waha (2015),[21] prospective cohort study	Germany (Aug 2006 – Aug 2009)	n = 276, 66.0, 27.5%	Structured interview	Clopidogrel (n=276)	Structured telephone questionnaire linked to hospital records	MACE (death, non-fatal MI): 20/153 no morphine, morphine 14/123	Median 16 months	Unadjusted. Exclusion criteria: prior fibrinolysis, cardiogenic shock, contraindications to CMR
Farag (2018),[22] prospective cohort study.	United Kingdom (Apr 2015 – June 2016)	n = 300, 64.0, 21.3%	Medical records	Clopidogrel (n=259) Ticagrelor (41)	Medical records, based on European Society of Cardiology guidelines or Bleeding Academic Research Consortium definition	No statistically significant difference in event rates In-Hospital Outcome Death: 2/82 no morphine, 4/218 morphine Re-infarction: 0/82 no morphine, 3/218 morphine Stroke: 0/82 no morphine, 3/218 morphine MACE: 2/82 no morphine, 10/218 morphine 30-day outcome: Death: 2/82 no morphine, 8/218 morphine Re-infarction: 0/82 no morphine, 6/218 morphine Stroke: 0/82 no morphine, 4/218 morphine MACE: 2/82 no morphine, 18/218 morphine	Median in-hospital stay 3.0 30 days	Unadjusted. Exclusion criteria: vomiting following DAPT loading pre-PPCI, intubation, unable to swallow, premorbid oral anticoagulation, those with known coagulation disorders, low platelet count, low haemoglobin, known active malignancy, inability to take DAPT.
Gwag (2017),[23] retrospective cohort study.	Republic of Korea (Jan 2008 – June 2014)	n = 307, 58.5, 19.8%	SMART-AMI-CMR Registry	Clopidogrel (n=299)	SMART-AMI-CMR Registry	No significant differences in MACE-free survival in crude or propensity score-matched analysis Death: 5/209 no morphine, 2/98 morphine MACE (cardiac death, recurrent MI, ischaemic stroke, coronary revascularisation following index procedure): 26/209 no morphine, 8/98 morphine MI: 5/209 no morphine, 1/98 morphine	20.6 months morphine, 28.4 months no morphine	Unadjusted. Exclusion criteria: 12 hours or more symptom to balloon time, medical treatment without primary PCI, previous history of MI, revascularisation.
Iakobishvili (2010),[10] retrospective cohort study	Israel (Mar 2008 – May 2008)	n = 765, 59.6, 18.9%	ACSIS database	Not specified Unclear if all patients were on a P2Y12 inhibitor	ACSIS database	At 30 days: Death: 6.7% no IVN, 3.1% IVN. Adjusted OR = 0.40; 95% CI 0.14-1.14, p=0.08 MACE (death, recurrent infarction, repeat ischaemia, stent thrombosis, CVA): 16.3% no IVN, 11.1% IVN. Adjusted OR = 0.69; 95% CI 0.42-1.16, p=0.16	30 days	Adjusted for age, gender, Killip class, previous MI, previous angina, previous CCF, renal failure, PVD, previous revascularisation, hypercholesterolemia, hypertension, T2DM, heart rate, systolic blood pressure, and propensity score for intravenous narcotic use, Exclusion criteria: transfer to other hospital
Kubica (2016),[7] RCT (IMPRESSION)	Poland (Aug 2014 – June 2015)	n = 70, 61.6, 27.0%	Randomised	Ticagrelor (n=70)	Not specified	In hospital: Death: 0/35 no morphine, 0/35 morphine MI: 0/35 no morphine, 0/35 morphine Stroke: 0/35 no morphine, 0/35 morphine MACE (death, MI, stent thrombosis, CVA): 0/35 no morphine, 1/35 morphine	In-hospital (average length of stay not specified)	Exclusion criteria: unbearable chest pain, request for analgesics, prior morphine administration during the current MI, treatment with any P2Y12 receptor inhibitor within 14 days, ongoing treatment with oral anticoagulant or chronic therapy with low

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								molecular weight heparin, active bleeding, Killip class III or IV, respiratory failure, coagulation disorders.
Lapostolle (2018),[24] post hoc analysis of RCT (ATLANTIC)	Algeria, Australia, Canada, Europe (Sep 2011 – Oct 2013)	n = 1858, 60.8, 19.8%	ATLANTIC trial database	Ticagrelor (n=1862)	ATLANTIC trial database	Within 24 hours of loading dose: Death: 6/937 no morphine, 10/921 morphine, OR 1.70; 95% CI 0.62-4.71, p=0.30 MI: 2/937 no morphine, 4/921 morphine, OR 2.04; 95% CI 0.37-11.18, p=0.41 MACE (death, MI, CVA, urgent revascularisation, definite stent thrombosis): 16/937 no morphine, 18/921 morphine, OR 1.15, 95% CI 0.58-2.26, p=0.69	24 hours	Exclusion criteria: per ATLANTIC trial. Not specified in publication.
McCarthy (2018),[25] retrospective cohort study	United States (Jan 2009 – July 2016)	n = 1287, 61.4, 25.6%	MGH Cardiac Catheterisation Database	Clopidogrel (n=909) Ticagrelor (n=290)	MGH Cardiac Catheterisation Database	Death in hospital stay: 4.18% no morphine, 7.54% morphine. Adjusted OR = 0.36; 95% CI 0.08-1.68, p=0.19 Propensity matched cohort of STEMI patients – adjusted OR death = 0.58; 95% CI 0.19-1.78, p=0.34	In-hospital (average length of stay no morphine 5.91 days, morphine 5.40 days)	Adjusted for age, sex, BMI, family history of coronary artery disease, shock at PCI, hypertension, T2DM, smoking, hypercholesterolemia, heart rate, systolic blood pressure, door to balloon time, prior CABG, CCF, CVA and renal impairment
Parodi (2015),[8] retrospective cohort study	Italy, Greece (not specified)	n = 300, 61.4, 22.7%	Various cohort studies	Ticagrelor (n=205) Prasugrel (n=95)	Not specified	In hospital stay: Death: 7/205 no morphine, 2/95 morphine Reinfarction: 1/205 no morphine, 1/95 morphine Stroke: 2/205 no morphine, 0/95 morphine	In-hospital (average not specified	Unadjusted. Exclusion criteria: age<18, active bleeding, previous CVA, administration of antiplatelet therapy in the week prior to the event, chronic anticoagulation, known haematological disorders, life expectancy <17 year, known severe liver or renal disease, haemodynamic instability.
Puymirat (2016),[9] retrospective cohort study (two cohorts)	France (FAST-MI 2010 Oct 2010 – Nov 2010; FAST-MI 2005 Oct 2005 – Nov 2005)	FAST-MI 2010 n = 2438, 63.3, 25.4% FAST-MI 2010 (pre-hospital thienopyridines only) n = 1108, 62.1, 22.1% FAST-MI 2005 n = 1726, 65.0, 29.9%	FAST-MI 2010 and 2005 registries	FAST-MI 2010: Clopidogrel (n=1726) Prasugrel (n=195) FAST-MI 2005: Clopidogrel (n=209) Not all patients were on P2Y12 inhibitor though this was separately analysed	FAST-MI 2010 and 2005 registries	FAST-MI 2010 (in-hospital): Death: 88/1985 no morphine, 6/453 morphine. Adjusted OR = 0.48; 95% CI 0.12-1.85, p=0.29 Recurrent MI: 14/1985 no morphine, 8/453 morphine. Adjusted OR 2.94; 95% CI 1.17-7.37, p=0.02 Death or recurrent MI: 99/1985 no morphine, 14/453 morphine. Adjusted OR 1.21; 95% CI 0.59-2.50, p=0.60 FAST-MI 2010 in patients receiving pre-hospital thienopyridines adjusted (in-hospital): Mortality: OR 0.28, p = 0.045 Recurrent MI: OR 1.35, p = 0.20 Stroke: OR 0.57, p = 0.29 One-year survival according to pre-hospital morphine use adjusted HR = 0.69, 95% CI 0.35-1.37, p=0.29 FAST-MI 2005 (in-hospital): Death: 103/1447 no morphine, 10/279 morphine. Adjusted OR = 0.48; 95% CI 0.21-1.10, p=0.08 Recurrent MI: 23/1447 no morphine, 3/279 morphine. Adjusted OR 0.75; 95% CI 0.21-2.66, p=0.65 In hospital death or recurrent MI: 118/1447 no morphine, 12/279 morphine. Adjusted OR 0.59; 95% CI 0.29-1.23, p=0.16	One year	Exclusion criteria: iatrogenic MI, ACS diagnosis invalidated, unstable angina with no cardiac biomarker increase. Adjusted for baseline characteristics and reperfusion therapy

ACS, acute coronary syndrome; CCF, congestive heart failure; CMR, cardiac magnetic resonance; CVA, cerebrovascular attack; DAPT, dual antiplatelet therapy; HR, hazard ration; IVN, intravenous narcotics; MACE, major adverse cardiovascular event; MI, myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; RCT, randomised controlled trial; TIA, transient ischaemic attack; T2DM, type 2 diabetes mellitus;

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