



Original Article

Effect of morphine use on oral P2Y12 platelet inhibitors in acute myocardial infarction: Meta-analysis



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ABSTRACT

Background: Morphine is the recommended analgesic in acute myocardial infarction (AMI). This recommendation has come under scrutiny because of possible slow uptake of oral antiplatelet agents. **Objective:** We performed a meta-analysis of all available studies in AMI patients treated with prasugrel or ticagrelor (P2Y12 inhibitors) that reported use of morphine prior to loading the antiplatelet agents to critically assess the safety of co-administration of morphine and the newer P2Y12 inhibitors.

Methods: Several sources were searched from inception to December 2017 with inclusion of eight studies, largely observational. Mean difference (MD) was calculated for continuous variables, and standardized mean difference (SMD) for platelet function was assessed by the various platelet assays, 2 h after the loading dose of oral P2Y12 inhibitors.

Results: Higher platelet activity was noted among morphine group [SMD = 0.8, 95% confidence interval (CI) = 0.4–1.1, $p < 0.01$]. Morphine use caused higher odds of “high residual platelet reactivity” at 2 h (odds = 3.3, 95% CI = 2.2–5.1, $p < 0.01$). Ticagrelor reached a lower plasma concentration in morphine group (MD = –481.8 ng/ml, 95% CI = –841.2 to –122.4 ng/ml, $p < 0.01$) with a higher vomiting rate (odds = 5.3, 95% CI = 2.5–11.1, $p < 0.01$). However, the composite of in-hospital mortality, stroke, and reinfarction was not significantly different between the groups ($p = 0.83$).

Conclusion: Co-administration of morphine with P2Y12 inhibitors possibly decreases their efficacy in platelet inhibition. However, this did not translate into higher adverse outcomes because of low event rates, inadequate for analysis. A large randomized study is needed to evaluate the narcotic-P2Y12 interaction.

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1. Introduction

Morphine is the current first-line recommended medication for pain management in patients with acute coronary syndrome (ACS) (Level of Evidence B, ACC/AHA guidelines).^{1–3} Fentanyl is also widely used for moderate sedation during percutaneous coronary

intervention (PCI). The goal is to reduce pain, suffering, anxiety, and dyspnea.^{2–4} Pain relief could help ease the sympathetic drive.⁵ A concern has been raised that narcotic co-administration with P2Y12 inhibitors may reduce the levels of these orally administered antiplatelet agents through gastrointestinal transit delay.⁶ This is especially important in the immediate post-PCI period when the thrombogenic potential is the highest. The updated 2017 European Society of Cardiology guidelines on acute myocardial infarction (AMI) management has highlighted these concerns.⁶ With the widespread use of newer P2Y12 inhibitors, there is a need to assess the safety of concurrent pain management with morphine during AMI, given the above interaction. Several studies have investigated the effects of concurrent use of morphine and P2Y12 inhibitors on adverse cardiovascular outcomes in patients with AMI; however, there is lack of clarity on the judicious use of morphine in this patient population.

Abbreviations: STEMI, ST-elevation myocardial infarction; AMI, acute myocardial infarction; PCI, percutaneous coronary intervention; MD, mean difference; SMD, standardized mean difference; ACS, acute coronary syndrome; PRU, platelet reactivity units; VASP, vasodilator-associated stimulated phosphoprotein; PRI, platelet reactivity index; HRPR, high residual platelet reactivity; C_{max} , maximum ticagrelor concentration; AUC, area under curve; MACE, major adverse cardiovascular events; RCT, randomized controlled trial; NRS, nonrandomized studies; NSTEMI, Non-ST elevation myocardial infarction.

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2. Methods

2.1. Data source and search strategy

The systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.⁷ We searched PubMed, EMBASE, Cochrane Central, clinicaltrials.gov databases, without any language restrictions, from inception to April 2018. An experienced medical reference librarian assisted in the search. Two authors (GV, AK) independently reviewed each article for eligibility for inclusion. The two above authors independently extracted data from the included studies, including demographic, laboratory, and outcome data. Any disagreements were solved through consensus and/or by the third reviewer (SG).

The following keywords were used for search in various combinations: morphine, fentanyl, opioid, prasugrel, ticagrelor, clopidogrel, platelet function test, myocardial infarction, myocardial ischemia, and ACS. National and international conferences proceedings were searched for related abstract publications. Search terms were devised using wildcards to account for variations in spellings. Retrieved articles were then screened for any mention of opioid use to identify pertinent articles. References in review articles were screened manually for potential appropriate articles. The criteria for inclusion included: prospective studies of platelet function (randomized, observational, or sub-studies), and documentation of narcotic use for the purpose of pain relief in AMI prior to loading dose of antiplatelet agents.

2.2. Data extraction

Morphine use was defined as morphine administration prior to the initial oral P2Y12 loading during PCI. However, the criteria for morphine use was not standardized to a particular dose or timing. The remaining patients without documented morphine use, as defined above, were counted under no-morphine category. Patient demographic data, past medical history, medication use, and outcome data were noted if provided in the studies. Platelet function was assessed using platelet function tests. In specific, three different tests are available for platelet function—VerifyNow test measures platelet reactive units (PRU), vasodilator-associated stimulated phosphoprotein (VASP) assay measures platelet reactivity index (PRI), and various forms of platelet aggregometry—electrical impedance, light, and chemical measured in Units (U)—measure platelet aggregation. VerifyNow is performed at the point-of-care and uses photometric assessment of platelet aggregation. VASP is a laboratory test involving flow-cytometric analysis of platelet vasodilator-stimulated phosphoprotein phosphorylation while platelet aggregometry involves adenosine diphosphate (ADP)-induced platelet aggregation and assessment of light or electrical transmission/impedance. Higher values in all these tests suggest higher platelet reactivity. In the context of AMI, they are used to assess patient's platelet reactivity to antiplatelet medications including P2Y12 inhibitors. The cut-off for high residual platelet reactivity (HRPR) was defined as per choice of platelet function test—PRU >208, PRI >50%, and aggregometry >46 U, respectively.

Pharmacokinetic data were only available for ticagrelor in the form of maximum ticagrelor concentration (C_{max}). Graph of plasma concentration to time was reported as area under curve (AUC); however, the period of assessment varied from 12 h after the loading dose (AUC_{0-12})⁸ to the time for last measurable concentration (AUC_{0-t}).⁹ Metabolite assessment (AR-C124910XX) was excluded from the assessment.

2.3. Bias assessment

Risk of bias was assessed using Risk of Bias in Nonrandomized Studies of Interventions tool¹⁰ for nonrandomized study data. Studies were evaluated on the following domains: confounding bias, selection bias, classification of intervention bias, deviation from intended intervention bias, missing data bias, outcome measurement bias, and selective reporting bias. For the randomized trials, the Cochrane risk of bias tool was used.¹¹ This tool was used to assess the domains of adequacy of random sequence generation, allocation concealment, blinding of participants and physicians, blinding of outcome assessment, selective reporting, and other potential bias. Each domain was then scored as low, moderate, serious, or critical risk of bias.

2.4. Statistical analysis

Continuous data were extracted as mean or median. Median with interquartile range was converted to mean and standard deviation.¹¹ For continuous variables including C_{max} and AUC, the mean difference (MD) was calculated between morphine and non-morphine groups (fixed-effects model). Standardized mean difference (SMD) was calculated for platelet function assessed by the various assays, at 2 h time-point after the loading dose of antiplatelet agent (random-effects model). The presence of HRPR, as defined above, after 2 h of oral P2Y12 inhibitor loading was counted as events. To account for the variability in study design, result reporting, and outcome assessment, only data measured at the same time-point following the oral P2Y12 inhibitor loading were used for quantitative analysis. When more than one platelet function test were used in the same study, the test with the most number of patient data was used.

Clinical outcomes included in-hospital mortality, stroke, and reinfarction/stent thrombosis in both groups. These outcomes were combined together into a composite endpoint—major adverse cardiovascular events (MACE), because none of the studies were powered to assess each outcome independently. Meta-analysis was performed using a fixed-effects model when heterogeneity was not significant and with random model if heterogeneity was significant. Odds ratio (OR) was calculated from the analyses. Review Manager v5.2 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2014) was used for all statistical analyses. The fixed-effects model was used for all analyses except platelet function assays where the random-effect model was used. Heterogeneity was assessed using I^2 statistic.¹² Publication bias was estimated using the funnel plot.¹¹ Finally, to assess the validity of the results from observational studies, a sensitivity analysis was performed by excluding the randomized controlled trial (RCT) from the analysis.

3. Results

Literature search identified 72 individual studies of which 8 studies were eligible for analysis with a total 752 AMI patients^{3,8,9,13–17} (Fig. 1). An attempt was also made to gather the non-reported data by contacting the corresponding authors via email. No response was obtained.

Table 1 summarizes the characteristics of studies including the study design, whereas Table 2 has the baseline characteristics regarding patients included in the individual studies when available. Studies were excluded if performed on healthy subjects,^{18,19} incomplete data,^{9,16} or not exclusively enrolling AMI patients.^{20,21} The eligible studies included one RCT,⁸ three prospective observational studies,^{13–15} three post-hoc analyses of individual RCTs,^{9,16,17} and one integrative analysis of five prospective observational studies performed by a single group.³ One study¹⁵ used abciximab

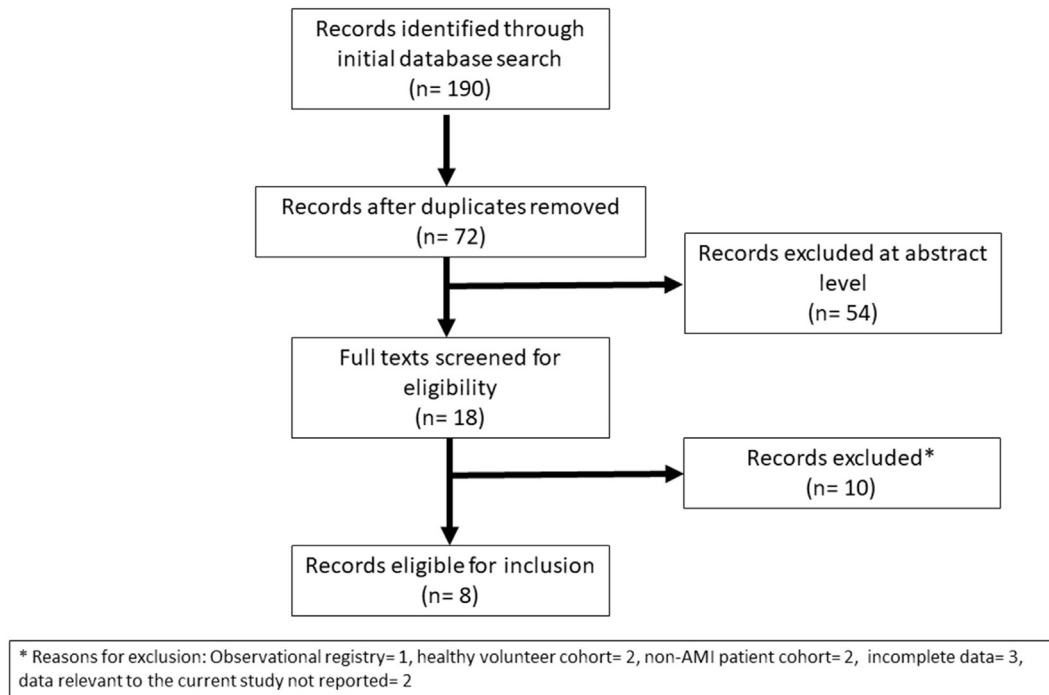


Fig. 1. Flowsheet for inclusion into the analysis (PRISMA flowsheet). AMI, acute myocardial infarction; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

as a bridge to counteract the effects of morphine on P2Y12 inhibitor absorption; only the data from those patients who did not receive abciximab were used for our analysis. Clopidogrel use was reported in one study,²² ticagrelor was the P2Y12 inhibitor used in three studies,^{8,9,16} and prasugrel was used in three studies,^{14,15,17} whereas two studies reported usage of both ticagrelor and prasugrel^{3,13} (ticagrelor = 493 patients, prasugrel = 259 patients). Morphine use was reported in 328 patients, and the remaining 424 patients were included in the non-morphine group. All studies included only patients who presented with ST-elevation myocardial infarction (STEMI) except one study⁸ which also included patients with non-ST-elevation myocardial infarction (NSTEMI). There was no difference in the risk factors (age, hypertension, and diabetes) between morphine and non-morphine groups (Supplemental Fig. 1). There was also no difference in the rates of prior PCI and history of MI (data not shown).

The results of bias assessment are summarized in Table 3A and Fig. 2A for nonrandomized studies, and in Table 3B and Fig. 2B for the randomized study (RCT). The overall bias in the studies was found to be low; however, all the studies were limited by confounding.

3.1. Pharmacodynamic effect

Five studies^{3,8,13,15,17} reported the effect of morphine use on platelet function; two studies used the VerifyNow test,^{3,13} one used electrical impedance aggregometry,¹⁵ one used VASP test,¹⁷ and one used all three tests.⁸ Since the platelet function test used by different studies and their cut-offs for HRPR were not uniform, there was significant heterogeneity in reporting ($I^2 = 57\%$, $p = 0.04$). Morphine use was associated with higher platelet function at 2 h suggestive of decreased inhibition of the platelet pool as compared with non-morphine group (SMD = 0.77, 95% CI = 0.46–1.08, $p < 0.001$) (Fig. 3A). Similarly, four studies^{3,8,14,15} reported the HRPR rates following P2Y12 inhibitor loading at 2 h. Morphine was

associated with higher incidence of HRPR at 2 h with an odds ratio of 3.37 (95% CI 2.20–5.15, $p < 0.001$). There was no significant heterogeneity in between the studies ($I^2 = 17\%$, $p = 0.30$) (Fig. 3B).

Sensitivity analysis suggested similar findings even after exclusion of the included RCT⁸ in terms of platelet function (SMD = 0.83, 95% CI = 0.38–1.27, $p < 0.001$). Similarly for HRPR, exclusion of the RCT yielded similar results (odds ratio = 3.09, 95% CI = 1.90–5.02, $p < 0.001$).

3.2. Pharmacokinetic effect

Two studies^{8,9} reported the effect of morphine on the pharmacokinetics of ticagrelor loading. Ticagrelor C_{max} was significantly lower in the morphine group (MD = -481.84 ng/ml, 95% CI = -841.24 to -122.43 ng/ml, $p = 0.009$) (Fig. 4A). No heterogeneity was noted ($I^2 = 0\%$). Moreover, AUC of plasma concentration to time for ticagrelor was also significantly lower within the morphine group (SMD = -0.46, 95% CI = -0.84 to -0.08, $p = 0.02$) (Fig. 4B).

3.3. Clinical outcomes with morphine use

Three of the included studies^{3,8,13} noted a higher incidence of nausea/vomiting with morphine use with an OR of 5.39 (95% CI = 2.59–11.18, $p < 0.001$) (Fig. 5A). There was no heterogeneity between studies ($I^2 = 0\%$). Exclusion of the RCT⁸ did not alter the findings significantly (OR = 5.39, 95% CI = 2.54–11.43, $p < 0.001$).

In terms of in-hospital MACE, three studies reported a non-zero event rate of combined composite of re-infarction, stroke, and mortality. The meta-analysis showed no difference in in-hospital MACE between the morphine and non-morphine groups (OR = 0.90, 95% CI = 0.36–2.26, $p = 0.83$) (Fig. 5B). No heterogeneity was noted ($I^2 = 0\%$). The results were consistent even after exclusion of the RCT⁸ (OR = 0.79, 95% CI = 0.30–2.12, $p = 0.64$).

Funnel plots are noted in Supplemental Fig. 2.

Table 1
Description of studies included in analysis.

Study	Study type	Population	Number of patients	Aspirin dose	P2Y12 inhibitor used	Median narcotic dose	Platelet function assessment	HRPR cut-off
Bellandi et al. ¹³	Prospective observational	STEMI	182 (morphine = 74, non-morphine = 108)	300–500 mg	Ticagrelor 180 mg = 131 and prasugrel 60 mg = 51	Morphine 6 ± 3 mg	VerifyNow	PRU ≥ 208
Flierl et al. ¹⁴	Prospective observational	STEMI	50 (morphine = 33, non-morphine = 15, unclear = 2)	500 mg	Prasugrel 60 mg	Morphine (1–17.5 mg)	VASP	PRI > 50%
Franchi et al. ⁹	Post-hoc of randomized trial	STEMI	46 (morphine = 16, non-morphine = 30)	325 mg	Ticagrelor (180 mg = 16, 270 mg = 15, 360 mg = 15)	Morphine (dose unclear)	VASP and VerifyNow	PRI > 50%, PRU > 208
Kubica et al. ⁸	Single center, randomized, placebo controlled	Acute MI (STEMI 45 and NSTEMI 29)	74 (morphine = 37, non-morphine = 37)	300 mg	Ticagrelor 180 mg	Morphine 5 mg	VASP, VerifyNow, Electrode aggregometry	PRI > 50%, PRU > 208 and AUC > 46 U respectively
Parodi et al. ⁴	Integrative analysis of 5 independent studies	STEMI	300 (morphine = 95, non-morphine = 205)	300–500 mg	Ticagrelor 180 mg = 205 and prasugrel 60 mg = 95	Morphine 4 mg (2–6 mg)	VerifyNow	PRU ≥ 208
Siller-Matula et al. ¹⁵	Prospective observational	STEMI	32 (morphine = 19, non-morphine = 13)	250 mg	Prasugrel 60 mg	Variable from 5 to 15 mg morphine	Impedance aggregometry	AUC > 46 Units
Silvain et al. ¹⁶	Post-hoc of the randomized ATLANTIC trial ²³	STEMI	37 (morphine = 22, non-morphine = 15)	All patients received but doses not available	Ticagrelor 180 mg (21 prehospital, 16 in-hospital)	Morphine (dose unclear)	VASP and VerifyNow	PRI > 50% or PRU > 235
Zeymer et al. ^{17,24}	Post-hoc of the randomized ETAMI trial	STEMI	62 (morphine = 32, non-morphine = 30)	500 mg iv or 300 mg oral	Clopidogrel 600 mg = 31 and 60 mg prasugrel = 31	Morphine (dose unclear)	VASP	PRI > 50%

STEMI, ST-elevation myocardial infarction; AMI, acute myocardial infarction; VASP, vasodilator-associated stimulated phosphoprotein; ATLANTIC trial, Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery; ETAMI trial, Early thienopyridine treatment to improve primary PCI in patients with acute myocardial infarction; PRI, platelet reactivity index; PRU, platelet reactive units; AUC, area under curve; PCI, percutaneous coronary intervention; HRPR, high residual platelet reactivity.

Table 2
Baseline demographic data of the studies when available.

Study	Morphine use	No. of patients	Age	Male	BMI	HTN	DM	Prior MI	Prior PCI/CABG	Culprit vessel/location of infarction
Parodi et al. ⁴	Morphine	95	62.0	73%	26.8	48%	15%	8%	8%	50% Anterior infarction
	Non-morphine	205	61.1	79%	28.1	54%	11%	7%	6%	42% Anterior infarction
Bellandi et al. ²⁵	Morphine	74	64	73%	27	55%	16%	8%	7%	1% Left main, 45% LAD, 15% LCx, and 38% RCA
	Non-morphine	108	64	76%	27	60%	23%	8%	9%	3% Left main, 40% LAD, 18% LCx, and 36% RCA
Flierl et al. ¹⁴	Morphine	33	56	90%		56%	22%			
	Non-morphine	15								
Kubica et al. ⁸	Morphine	35	60.7	66%	27.6	43%	23%	14%	11%	
	Non-morphine	35	62.5	80%	27.4	60%	14%	23%	26%	
Siller-Matula et al. ¹⁵	Morphine	19	58	94%		56%	17%	22%	18%	
	Non-morphine	13	63	84%		72%	9%	18%	9%	

LAD, left anterior descending artery; LCx, left circumflex artery; RCA, right coronary artery; PCI, percutaneous coronary intervention; BMI, body mass index; HTN, hypertension; DM, diabetes; MI, myocardial infarction; CABG, coronary artery bypass grafting.

4. Discussion

The salient findings of our analysis suggest (1) decreased platelet inhibition when morphine was administered prior to oral P2Y12 inhibitor use, (2) higher incidence of residual platelet reactivity with morphine use, (3) decreased levels of plasma ticagrelor if administered after morphine use, (4) increased incidence of nausea/vomiting with morphine use which may cause expulsion of oral agents including platelet inhibitors, and (5) no conclusion could be drawn regarding MACE because of low event rates and inadequacy of the analysis.

Our analysis suggests decreased platelet inhibition and consequently higher residual platelet reactivity with co-administration of morphine with P2Y12 inhibitors. No difference was noted in the prevalence of risk factors (age, hypertension, and diabetes) among both the groups (Supplemental Fig. 1). However, the available data does not allow to draw conclusions regarding the effect on overall clinical outcome. This is mostly because of the small size of the included studies lacking sufficient power to detect a difference in hard outcomes. It underlines the lack of large-scale randomized studies to address this important question which could have important clinical implications.

Similar results were reported by the observational CRUSADE registry of high-risk ACS patients receiving clopidogrel.²³ The authors reported a higher rates of adverse outcomes among patients receiving morphine (MI = 3.8% vs 3.0%, cardiogenic shock = 3.8% vs 2.3%, in-hospital death = 5.5% vs 4.7%, and composite of death or MI = 8.5% vs 7.1%). It is also possible that interaction between morphine and clopidogrel, with its requirement of 2-step metabolic activation, may be more significant. CRUSADE registry was excluded from our analysis because of lack of pharmacokinetic/dynamic data on platelet function.

Along with higher HRPR rates within the morphine group, Bellandi et al.¹³ noted lower incidence of ST segment resolution at 30 min in the morphine group ($p = 0.047$). The lowering of antiplatelet effect has also been noted in patients undergoing routine angiography and PCI and with the use of other narcotic analogs.^{21,24} In this study, higher HRPR rates were noted with fentanyl after 2 h (22% vs 3%, $p = 0.02$).

4.1. Solutions attempted

Flierl et al.¹⁴ reported a prospective observational study of 50 prasugrel-treated STEMI patients who received morphine, with or without metoclopramide as an antiemetic. Among morphine treated patients, use of metoclopramide resulted in lower HRPR rates though this was not a significant finding. Siller-Matula et al.¹⁵

suggested the use of abciximab to counteract the delay in onset of antiplatelet effect.

There have been other attempts to counteract the adverse effect of morphine, while keeping the analgesic function intact. A prospective, randomized cross-over trial was presented in the American Heart Association meeting in 2016.²⁵ The study aimed to assess the possible role of methylnaltrexone, a peripheral opioid receptor antagonist commonly used for opioid induced constipation, in preventing slow P2Y12 inhibition. This study ($n = 30$ patients) failed to show any benefit in plasma ticagrelor concentration with intravenous methylnaltrexone over placebo after morphine use in patients with coronary artery disease. A randomized study (Methylnaltrexone as a Method to Improve Ticagrelor Uptake in Morphine Treated STEMI Patients)²⁶ is currently registered to further investigate this effect. Some other randomized studies are being performed to understand any possible role of naloxone (NCT02939248)²⁷ and metoclopramide (NCT02939235)²⁸ to alleviate this interaction.

4.2. Implications for clinical practice

In addition to advancing our understanding of morphine-P2Y12 interaction, our results could potentially influence current clinical practice. Until more data are available, judicious use of morphine with objective assessment of pain should be routinely practiced in a protocol-driven manner. As suggested in the European Society of Cardiology guidelines,⁶ delayed onset of antiplatelet effects afforded by morphine use could potentially result in early treatment failure.

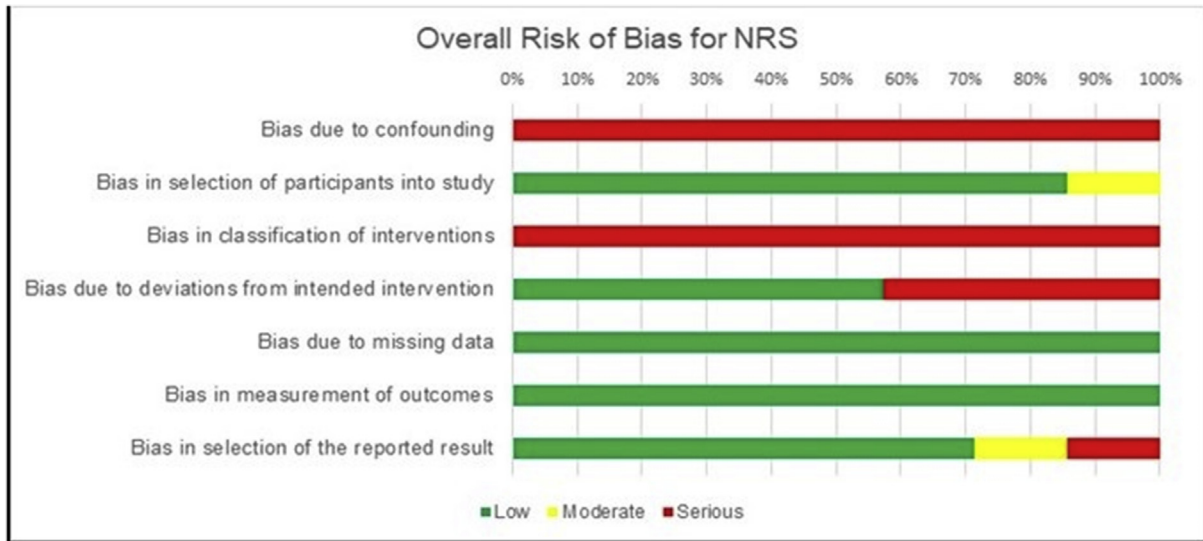
Consideration of intravenous antiplatelet/anticoagulation agents for bridging the narcotic administered patients will also be helpful. A recent study¹⁵ suggested that co-administration of abciximab with P2Y12 inhibitors may counteract the increased platelet activity because of morphine loading. The CHAMPION PHOENIX trial²⁹ suggested cangrelor as an effective intravenous antiplatelet agent during PCI. It will be interesting to assess the subset of patients who received narcotics for pain relief in this study cohort, and any beneficial effect cangrelor may have played as a bridge to oral antiplatelet agents. However, it has to be noted that the results of the present study do not show any increase in adverse events with morphine use.

4.3. Implications for research

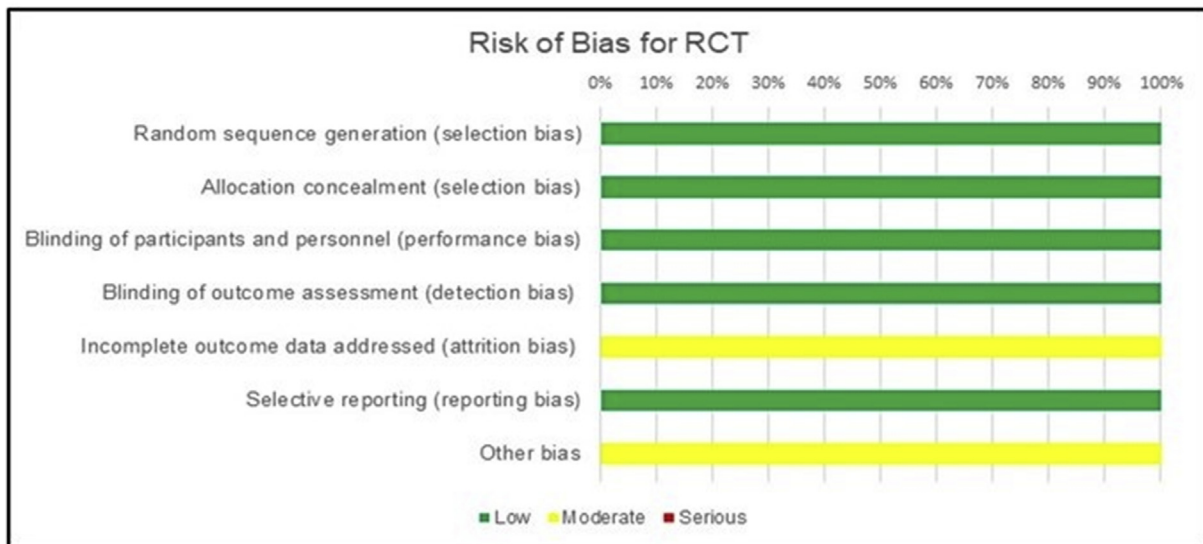
Future studies should be designed to assess the dose–response, and the effect of time of administration of morphine on platelet activity. In addition, these studies should assess clinical outcomes such as stent thrombosis, target lesion revascularization, target

Table 3A
Risk of bias in nonrandomized studies.

Study type: nonrandomized studies							
Author	Bias due to confounding	Bias in selection of participants into study	Bias in classification of interventions	Bias due to deviations from intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result
Bellandi et al. ¹³	SERIOUS Not adjusted for baseline pain scores and comorbidities.	LOW Consecutive patients	SERIOUS Dose, timing, frequency, and setting of morphine use was not clearly defined or blinded	LOW No deviations beyond usual care	LOW All patients available	LOW Objective lab tests used for outcome assessment	LOW Required data reported
Flierl et al. ¹⁴	SERIOUS Not adjusted for baseline pain scores, comorbidities.	LOW Consecutive patients	SERIOUS Dose, timing, frequency, and setting of morphine use was not clearly defined.	SERIOUS Metoclopramide co-intervention in some patients	LOW Two patients without morphine data	LOW Objective lab tests used for outcome assessment	MODERATE Some selective reporting of assessed results
Franchi et al. ⁹	SERIOUS Not adjusted for baseline pain scores and comorbidities.	LOW Substudy of randomized study	SERIOUS Dose, timing, frequency, and setting of morphine use was not clearly defined.	SERIOUS Variable loading dose of ticagrelor (as per the actual design of trial)	LOW All patients available	LOW Objective lab tests used for outcome assessment	LOW Required data reported
Parodi et al. ⁴	SERIOUS Not adjusted for baseline pain scores and comorbidities.	MODERATE Unclear if consecutive patients used	SERIOUS Dose, timing, frequency, and setting of morphine use was not clearly defined.	LOW No deviations beyond usual care	LOW All patients available	LOW Objective lab tests used for outcome assessment	LOW Required data reported
Siller-Matula et al. ¹⁵	SERIOUS Not adjusted for baseline pain scores and comorbidities.	LOW Substudy of randomized study	SERIOUS Dose, timing, frequency, and setting of morphine use was not clearly defined.	LOW No deviations beyond usual care (patients who received abciximab were selectively excluded from the meta-analysis)	LOW All patients available	LOW Objective lab tests used for outcome assessment	LOW Required data reported
Silvain et al. ¹⁶	SERIOUS Not adjusted for baseline pain scores and comorbidities.	LOW Substudy of randomized study	SERIOUS Dose, timing, frequency, and setting of morphine use was not clearly defined.	SERIOUS Prehospital and hospital administration of ticagrelor was not adjusted between groups	LOW All patients available	LOW Objective lab tests used for outcome assessment	SERIOUS Selective reporting of results
Zeymer et al. ^{17,24}	SERIOUS Not adjusted for baseline pain scores and comorbidities.	LOW Substudy of randomized study	SERIOUS Dose, timing, frequency, and setting of morphine use was not clearly defined.	LOW No deviations beyond usual care (clopidogrel administered patients were selectively excluded from the meta-analysis)	LOW All patients available	LOW Objective lab tests used for outcome assessment	LOW Required data reported



A



B

Fig. 2. A: Graphical representation of risk of bias in non-randomized study. B: Graphical representation of risk of bias in the randomized study. NRS, nonrandomized study; RCT, randomized controlled trial.

Table 3B
Risk of bias in the randomized study.

Study type: randomized study							
Author	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data addressed (attrition bias)	Selective reporting (reporting bias)	Other bias
Kubica et al. ⁸	LOW Random Allocation Software used	LOW Random Allocation Software used	LOW Blinded personnel (or investigators), unclear but presumed blinding of patients	LOW Objective lab tests used for outcome assessment	MODERATE One patient in each group without results. Results of all three platelet studies not available for all patients	LOW Required data reported	MODERATE Co-intervention with fentanyl for moderate sedation not reported. Alternate pain control strategy or crossover patients not reported.

Table 4

Ongoing studies, data obtained from clinicaltrials.gov. Last accessed 4/3/2018.

Serial Number	Title	Recruitment	Conditions	Locations	Registration number
1	Methylnaltrexone as a Method to Improve Ticagrelor Uptake in Morphine Treated STEMI Patients ²⁶	Recruiting	STEMI	Sweden	NCT02942550
2	Effects of Morphine on Loading-dose Ticagrelor in Patients With ST-segment Elevation Myocardial Infarction ³¹	Recruiting	STEMI	China	NCT02913469
3	Influence of Naloxone on Ticagrelor Pharmacokinetics and Pharmacodynamics in Patients With Unstable Angina Pectoris on Concomitant Treatment With Morphine ²⁷	Recruiting	Unstable Angina	Poland	NCT02217881
4	Influence of Metoclopramide on Ticagrelor Pharmacokinetics and Pharmacodynamics in Patients With Unstable Angina Pectoris on Concomitant Treatment With Morphine ³²	Recruiting	Unstable Angina	Poland	NCT02217882
5	Platelet Inhibition After Pre-hospital Ticagrelor Using Fentanyl Compared to Morphine in Patients With ST-segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention ³³	Completed	AMI	Switzerland	NCT02217883
6	Fentanyl and Crushed Ticagrelor in Percutaneous Coronary Intervention ³⁰	Not yet recruiting	PCI	United States	NCT03476369

STEMI: ST-elevation myocardial infarction, AMI: acute myocardial infarction, PCI: percutaneous coronary intervention.

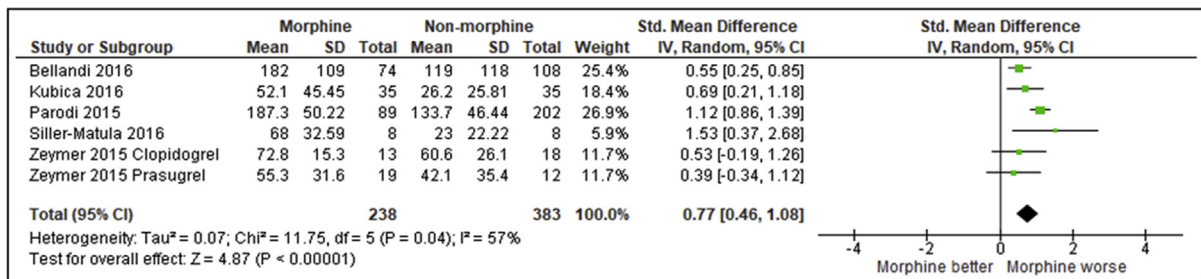
vessel revascularization, myocardial infarction, and mortality. Non-morphine agents such as methylnaltrexone or metoclopramide can be studied to counter the gastrointestinal delay.^{14,26,28} The use of intravenous P2Y12 as a loading agent followed by oral P2Y12 or anticoagulants needs to be further explored.²⁹ We also await the results of ongoing or recently concluded trials across the globe registered in the clinicaltrials.gov website, as mentioned in Table 4.^{26,27,30–33}

4.4. Limitations

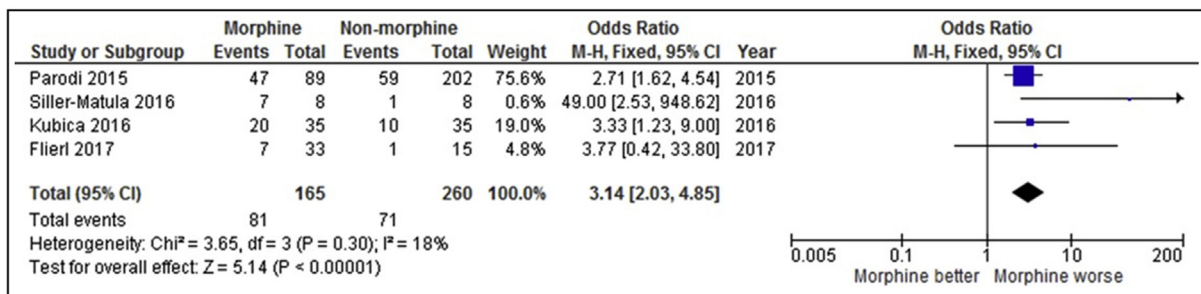
Our analysis has several limitations. The analysis was largely based on non-randomized studies. The time difference from morphine use to oral P2Y12 inhibitor loading and the morphine dose was not known in most studies. The following confounders were not addressed appropriately: baseline pain scores or pain

tolerance (more likely to request morphine), hypotension/shock (less likely to receive morphine), prior morphine use (more likely to request morphine), non-verbal/sedated patients (less likely to receive morphine), and variations in hospital or individual physician practice because of non-protocol driven use of morphine. A potential time-varying confounder was the residual pain score after the intervention which may have resulted in higher cumulative morphine dose administration and/or cross-over in some patients.

The platelet activity may also be affected by several factors leading to delay in absorption such as slow gastrointestinal transit in patients with gut ischemia, pretreatment hypotension/shock, improper technique of administration, and baseline gastrointestinal disturbances such as gastroparesis or vomiting, and this may be independent of morphine use. The effect of these factors on platelet activity can only be tested in a randomized controlled trial. In addition, there was lack of baseline platelet function testing prior



A



B

Fig. 3. A: Pharmacodynamic data—pooled analysis of platelet function tests. B: Pharmacodynamic data—pooled analysis of HRPR rates. SD, standard deviation; HRPR, high residual platelet reactivity; CI, confidence interval.

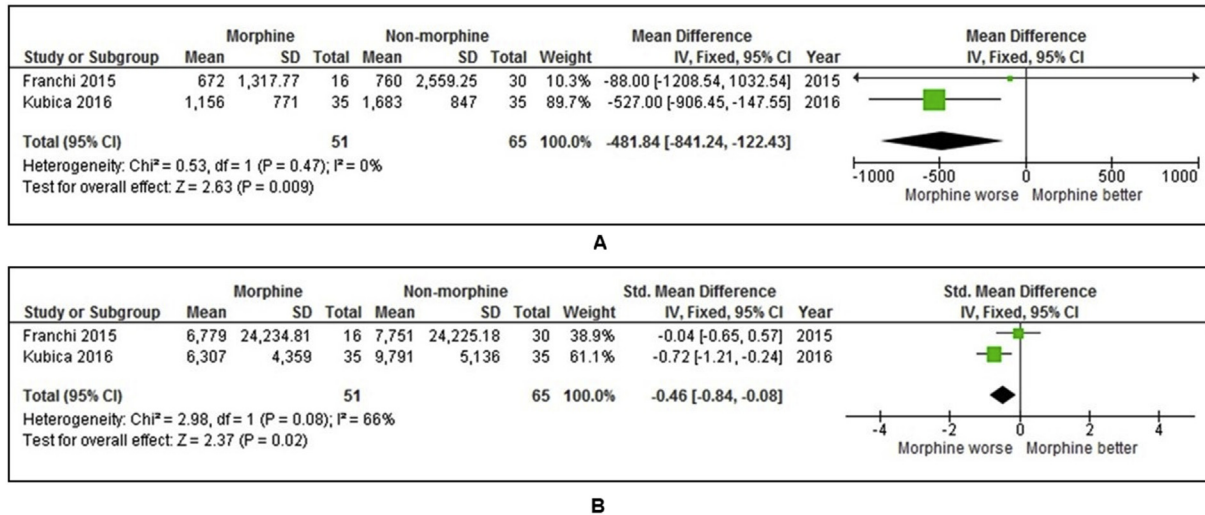


Fig. 4. A: Pharmacokinetic data—pooled analysis of Ticagrelor C_{max}. B: Pharmacokinetic data—pooled analysis of ticagrelor concentration AUC. SD, standard deviation; CI, confidence interval; AUC, area under curve.

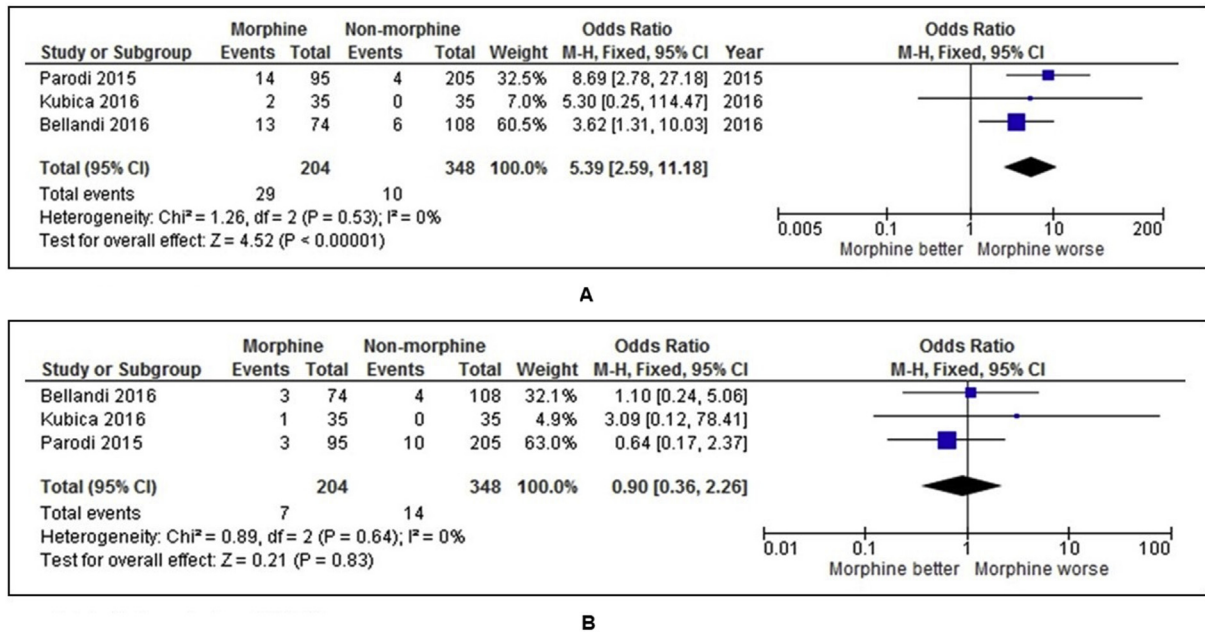


Fig. 5. A: Pooled analysis of vomiting rates. B: Pooled analysis of MACE. CI, confidence interval; MACE, major adverse cardiovascular event.

to oral P2Y12 inhibitor loading to check for adequacy of platelet inhibition. Finally, pharmacokinetic data were only available for ticagrelor.

5. Conclusions

Our meta-analysis suggests that co-administration of morphine with P2Y12 inhibitors decreases their efficacy in terms of inhibition of platelet activity. This did not translate into higher adverse clinical outcomes because of low event rates, inadequate for analysis. Our findings underline the need for an appropriately powered RCT to evaluate the clinical outcomes associated with narcotic-P2Y12 interaction.

Disclosures

No financial disclosures from any of the authors.

Conflicts of interest

All authors have none to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ihj.2019.03.003>.

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