

P2Y₁₂ Receptor Antagonists and Morphine A Dangerous Liaison?

Georgios Giannopoulos, MD; Spyridon Deftereos, MD; Fotios Kolokathis, MD;
Ioanna Xanthopoulou, MD; John Lekakis, MD; Dimitrios Alexopoulos, MD

Abstract—P2Y₁₂ receptor antagonists, concurrently administered with aspirin in what has come to be commonly called dual antiplatelet therapy, are a mainstay of treatment for patients with acute coronary syndromes. Morphine, on the contrary, is a commonly used drug in the acute phase of acute coronary syndromes to relieve pain—with the added potential benefit of attenuating acutely raised sympathetic tone. In current guidelines, though, morphine is recommended with decreasing strength of recommendation. One reason is that it raises concern regarding the potentially significant interaction with antiplatelet agents, leading to impaired inhibition of platelet activation. In any case, it is still considered a mandatory part of the inventory of available medications in prehospital acute myocardial infarction management. The goal of the present review is to present published evidence on morphine and its potential interactions with P2Y₁₂ receptor antagonists, as well as on the central issue of whether such interactions may underlie clinically significant effects on patient outcomes.

Key Words: acute coronary syndrome ■ antiplatelet drug resistance ■ antiplatelet therapy
■ inhibition ■ interaction ■ opioid

P2Y₁₂ receptor antagonists, concurrently administered with aspirin in what has come to be commonly called dual antiplatelet therapy, are a mainstay of treatment for patients with acute coronary syndromes (ACS), from the acute phase until at least 12 months after the index event.¹⁻³ Morphine, on the contrary, is a nonessential but commonly used drug in the acute phase of ACS to relieve pain—with the added potential benefit of attenuating acutely raised sympathetic tone.^{2,4} In current guidelines though morphine is recommended with decreasing strength of recommendation,^{2,3,5} one of the reasons being raised concerns regarding the potentially significant drug-to-drug interactions with antiplatelet agents, leading to impaired inhibition of platelet activation.⁶ In any case, it is still considered a mandatory part of the inventory of available medications in prehospital acute myocardial infarction management.⁷

The goal of the present review is to present published evidence on morphine and its potential interactions with P2Y₁₂ receptor antagonists, as well as on the central issue of whether such interactions may underlie clinically significant effects on patient outcomes.

P2Y₁₂ Antagonists and Morphine: Pharmacokinetic and Pharmacodynamic Evidence

Clopidogrel

There is substantial evidence that morphine affects clopidogrel kinetics and pharmacodynamic effects. In a sample of 24 healthy

volunteers, Hobl et al⁸ showed that intravenous morphine delayed the absorption of clopidogrel, although the area under the curve of clopidogrel concentration did not differ significantly between groups, and maximal inhibition of platelet aggregation. The delay was in the order of 1.75 hours: 3 versus 1.25 hours in morphine- versus placebo-treated subjects, respectively ($P < 0.001$). In addition, residual platelet reactivity was higher for ≤ 5 hours after morphine injection in comparison with placebo. In the setting of ACS, data are scarce. Zeymer et al have presented results from the ETAMI trial (Early Thienopyridine treatment to improve primary PCI in Patients with Acute Myocardial Infarction), suggesting that morphine was associated with higher platelet reactivity at 2 hours, but less so at 4 hours.⁹

Prasugrel and Ticagrelor

With respect to novel P2Y₁₂ antagonists, there is also evidence that morphine coadministration with prasugrel or ticagrelor may result in increased platelet reactivity. In the RAPID (Rapid Activity of Platelet Inhibitor Drugs) Primary Percutaneous Coronary Intervention (PCI) Study, which randomized 50 patients with ST-segment-elevation myocardial infarction (STEMI) to prasugrel or ticagrelor, morphine use was an independent predictor of high residual platelet reactivity, that is, platelet reactivity units ≥ 240 , 2 hours after the loading dose (odds ratio with morphine use 5.29; 95% confidence interval 1.44–19.49; $P = 0.012$), in a multivariable model adjusted for age, body mass index, diabetes mellitus, ejection fraction, cardiogenic shock, randomization arm, and baseline platelet

From the Second Department of Cardiology, National and Kapodistrian University of Athens, Attikon University Hospital, Greece (G.G., S.D., F.K., J.L., D.A.); and Department of Cardiology, University of Patras, University Hospital of Rio, Greece (I.X.).

Correspondence to Georgios Giannopoulos, MD, Second Department of Cardiology, National and Kapodistrian University of Athens, Attikon University Hospital, Greece. E-mail ggiann@med.uoa.gr; georgios.giannopolous@yale.edu

(*Circ Cardiovasc Interv.* 2016;9:e004229. DOI: 10.1161/CIRCINTERVENTIONS.116.004229.)

© 2016 American Heart Association, Inc.

Circ Cardiovasc Interv is available at <http://circinterventions.ahajournals.org>

DOI: 10.1161/CIRCINTERVENTIONS.116.004229

reactivity.¹⁰ However, the limitation of potential model overfitting should be noted, considering that a binary logistic regression model with 8 predictors was constructed in a sample with ≈ 25 positive outcomes for the dependent variable, that is, high residual platelet reactivity. Still, in a similar study in 50 STEMI patients, where a double loading dose of ticagrelor was used (RAPID 2 study), morphine use was again an independent predictor of high residual platelet reactivity (odds ratio with morphine use 4.49; 95% confidence interval 1.19–16.88; $P=0.026$) 1 hour after the loading dose, after adjustment for age, body mass index, diabetes mellitus, and baseline platelet reactivity.¹¹ In a randomized study, Kubica et al studied the effect of intravenous morphine 5 mg on the pharmacokinetic and pharmacodynamic profile of 180 mg ticagrelor in 70 patients with acute myocardial infarction.¹² Morphine was associated with lower total exposure to ticagrelor (36% smaller area under the concentration curve; $P=0.003$) and its active metabolite AR-C124910XX (37% smaller area under the concentration curve; $P=0.008$), delayed maximal plasma concentration (the median time to achieve maximal concentration of ticagrelor in plasma was 4 hours in patients who took morphine compared with 2 hours in controls), and lower maximal plasma concentration ($P=0.006$). At 2 hours after the loading dose, the proportion of patients with high residual platelet reactivity was 57% in the morphine group versus 29% in controls ($P=0.03$). Delayed onset of action when ticagrelor was coadministered with morphine was also reported in another study in 37 STEMI patients, where morphine administration was associated with significantly higher platelet reactivity at 1 and 6 hours after the loading dose of ticagrelor.¹³ The same, by and large, was shown for prasugrel in a small crossover study of 11 patients with a history of STEMI in the past 12 months,¹⁴ which showed increased platelet reactivity from 30 minutes \leq 2 hours after the loading dose when morphine was coadministered, both in terms of absolute platelet reaction units and percent platelet inhibition. The estimated time to achieve adequate platelet inhibition (platelet reactivity units <208) was 150 minutes with morphine versus 68 minutes without ($P=0.006$). Similarly, in a larger study, involving 108 STEMI patients treated with prasugrel, platelet reactivity at the end of primary PCI was 90.1 units in those who received morphine compared with 43.5 units in patients who did not ($P<0.001$).¹⁵ On the other hand, in the CRUSH study (Pharmacological Effects of Crushing Prasugrel in STEMI Patients),¹⁶ differences regarding the pharmacokinetic profile of the active metabolite of prasugrel were statistically non-significant with or without morphine, regardless of whether crushed or whole tablets were administered, both in terms of total exposure ($P=0.198$ and 0.286 , for whole and crushed tablets, respectively) and exposure over the first 2 hours ($P=0.459$ and 0.776 , for whole and crushed tablets, respectively) to the active metabolite. These findings are certainly hypothesis generating; however, the small sample size, the nonrandomized use of morphine, and the secondary or post hoc nature of most of these observations raise some doubt as to the true significance of the morphine effect on P2Y₁₂ receptor antagonist effectiveness in real life.

These limitations were addressed—at least in part—in a recently published report that studied the effect of morphine

use on platelet reactivity in 300 STEMI patients undergoing primary PCI.¹⁷ This report was based on a post hoc aggregated patient-level analysis of 5 studies (4 published^{10,11,18,19} and 1 previously unpublished).¹⁷ Patients who received morphine (95 of 300) had higher platelet reactivity overall and higher rates of high residual platelet reactivity at 2 hours (53% among those who took morphine versus 29% in those who did not; $P<0.001$). Morphine use was an independent predictor of high residual platelet reactivity after adjustment for age, body mass index, diabetes mellitus, systolic blood pressure, bivalirudin administration, and ticagrelor use. Importantly, this association remained significant after adjustment for morphine use propensity score to account for the nonrandomized administration of morphine, with an odds ratio for high residual platelet reactivity with morphine versus without of 1.89, 95% confidence interval 1.40 to 2.56. In another patient-level analysis of 207 STEMI patients from 5 studies, 82% of whom took ticagrelor or prasugrel, morphine use was a multivariable predictor of higher residual platelet reactivity: morphine resulted in a 0.334 increase in the log of expected platelet reactivity, corresponding to $\approx 40\%$ increased platelet reactivity, $P<0.001$.²⁰

Interestingly though, in a study of 24 healthy subjects, morphine was again associated with diminished total exposure to ticagrelor and delayed achievement of maximal plasma levels, but no significant effects were observed in terms of platelet reactivity.²¹ From the same group of researchers, a small crossover study showed in a group of 12 healthy volunteers only minimal effects of morphine on prasugrel absorption, resulting in reduced maximal plasma concentration without any significant interference with platelet inhibition.²² It should be noted though that observations from healthy volunteers may not apply in ACS patients, considering that in the absence of acute platelet overactivation (which is the case in ACS), lower or delayed exposure to the antiplatelet agents may suffice for adequate platelet inhibition. Studies in healthy individuals are of course useful, but should be supplemented by more real-world data from ACS populations. In this setting, Franchi et al evaluated different loading doses of ticagrelor and the effect of morphine in 52 STEMI patients.²³ Absorption of ticagrelor was slightly delayed by morphine (mean time to maximal concentration in plasma 5.6 versus 4.9 hours), and platelet reactivity levels were higher at 30 minutes after loading dose ($P=0.018$), but not significantly different at all other study time points between patients who took morphine and those who did not. Differences in rates of high residual platelet reactivity were not significant, and morphine was not an independent predictor of high on-treatment platelet reactivity. These ambivalent or negative results regarding the effect of morphine on the pharmacodynamics of novel P2Y₁₂ receptor antagonists cast doubt on the real magnitude of this interaction, as well as its relevance in different clinical scenarios. A concise description of published studies is provided in the Table.

Clinical Outcomes and Morphine

As important as the evidence regarding the effect of morphine on the pharmacokinetics and pharmacodynamics of P2Y₁₂ receptor antagonists may be, the real clinical issue lies in whether morphine use is actually associated with worse clinical outcomes. One of the first reports suggesting that there is truly a signal

Table. Studies on the Effect of Morphine on P2Y₁₂ Receptor Antagonist Pharmacokinetics and Pharmacodynamics

Study/Design	N	Clinical Setting	P2Y ₁₂ Receptor Antagonist	Morphine Effect on PK	Morphine Effect on PD
Hobl et al ⁸ /randomized for morphine, crossover, controlled	24	Healthy volunteers	Clopidogrel 600 mg	Increased T_{max}	Delayed maximal platelet inhibition
				Reduced C_{max} of active metabolite	Higher VASP-PRI for up to 4 h
				Reduced AUC (primary end point)	Delayed inhibition of platelet plug formation Abolishment of clopidogrel-induced prolongation of collagen/ADP-provoked closure time
Parodi et al ¹⁰ /nonrandomized for morphine, noncontrolled	50	STEMI, primary PCI	Prasugrel 60 mg, ticagrelor 180 mg	Not studied	Higher adjusted risk of high on-treatment platelet reactivity at 2 h
Parodi et al ¹¹ /nonrandomized for morphine, noncontrolled	50	STEMI, primary PCI	Prasugrel 60 mg, ticagrelor 360 mg	Not studied	Higher adjusted risk of high on-treatment platelet reactivity at 1 h
Kubica et al ¹² /randomized for morphine, 2 groups, controlled	70	STEMI and non-STEMI, PCI	Ticagrelor 180 mg	Increased T_{max} for ticagrelor and its active metabolite	Higher PRU at 0.5 and 3 h, VASP-PRI at 3 h and ADP reactivity at 0.5, 1, 2, 3, 4, 6, and 12 h
				Reduced C_{max} for ticagrelor and its active metabolite	Higher rate of high on-treatment platelet reactivity as defined by ADP reactivity at 0.5, 1, 2, and 3 h and by VASP-PRI at 1 and 2 h
				Reduced AUC for ticagrelor and its active metabolite (primary end point)	No significant effect on high on-treatment platelet reactivity as defined by the VerifyNow assay
Silvain et al ¹³ /nonrandomized for morphine, noncontrolled	37	STEMI, primary PCI	Ticagrelor 180 mg	Not studied	Higher VASP-PRI at 3 and 6 h post PCI
Thomas et al ¹⁴ /randomized for morphine, crossover, controlled	11	History of STEMI treated with PCI in previous 12 mo	Prasugrel 60 mg	Overall no significant effect on T_{max} , C_{max} or AUC for prasugrel and its active metabolite	Higher PRU at 0.5, 1, and 2 h (primary end point)
					Similar findings with light transmission aggregometry
Johnson et al ¹⁵ /nonrandomized for morphine, noncontrolled	106	STEMI, primary PCI	Prasugrel 60 mg	Not studied	Higher ADP reactivity at the end of PCI at 1 and 2 h post PCI
					No significant effect in ASPI and TRAP assays
Rollini et al ¹⁶ /nonrandomized for morphine, noncontrolled	50	STEMI, primary PCI	Prasugrel 60 mg	No significant effect on T_{max} , C_{max} or AUC	Not studied
Parodi et al ¹⁷ /nonrandomized for morphine, patient-level post hoc analysis of 5 studies, noncontrolled	300	STEMI, primary PCI	Ticagrelor 180 mg, 360 mg, prasugrel 60 mg	Not studied	Higher PRU at 2 h (primary end point) and at 4 h
					Higher rate of high on-treatment platelet reactivity as defined by the VerifyNow assay
Hobl et al ²¹ /randomized for morphine, crossover, controlled	24	Healthy volunteers	Ticagrelor 180 mg	Increased T_{max} for ticagrelor and its active metabolite (primary end point)	No significant effect
				Reduced C_{max} for ticagrelor and its active metabolite	
				Reduced AUC for ticagrelor and its active metabolite	
Hobl et al ²² /randomized for morphine, crossover, controlled	12	Healthy volunteers	Prasugrel 60 mg	No effect on AUC (primary end point), T_{max} Reduced C_{max}	No significant effect
Franchi et al ²³ /nonrandomized for morphine, noncontrolled	52	STEMI, primary PCI	Ticagrelor 180 mg, 270 mg, 360 mg	Increased T_{max} for ticagrelor and its active metabolite	No significant effect
				Lower AUC for ticagrelor and its active metabolite	

ADP indicates adenosine diphosphate; ASPI, arachidonic acid platelet aggregation; AUC, area under the curve; C_{max} , maximal concentration in plasma; PCI, percutaneous coronary intervention; PD, pharmacodynamics; PK, pharmacokinetics; PRU, P2Y₁₂ reactivity units; STEMI, ST-segment–elevation myocardial infarction; T_{max} , time to maximal concentration in plasma; TRAP, thrombin receptor activating peptide; and VASP-PRI, vasodilator-stimulated phosphoprotein platelet reactivity index.

of a deleterious effect of morphine came from the CRUSADE registry (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines).²⁴ Among 57039 patients with non-STEMI, 17003 received morphine. The raw data analysis showed increased risk for clinical events associated with morphine use, including higher in-hospital mortality (odds ratio 1.22, 95% confidence interval 1.10–1.34). After extensive adjustment for a large array of clinical and demographic risk factors, this association persisted (odds ratio 1.48, 95% confidence interval 1.33–1.64) and was consistent across various patient subgroups (Figure 1). The same result was obtained in a propensity-matched subcohort of 33972 patients (odds ratio 1.41, 95% confidence interval 1.26–1.57). These observations are certainly compelling; however, there are several important limitations. This was a registry—not a randomized study of morphine—and as a result, there were significant differences in the clinical and demographic background between patients who received morphine and those who did not. Multivariable adjustment and propensity score analysis may have remedied this, at least in part, but the possibility of a residual effect of unaccounted confounders cannot be discounted. In addition, patient treatment cannot possibly be considered to be current with 2016 standards, taking into account that only $\approx 40\%$ of patients were treated with a P2Y₁₂ receptor antagonist (clopidogrel) and just 66% were catheterized and 37% had a PCI performed during the index hospitalization, which is low considering that 88% had positive cardiac markers. In another study in 276 STEMI patients treated with primary PCI, morphine use was an independent predictor of having a myocardial salvage index (measured by gadolinium-enhanced magnetic resonance imaging) lower than the median

(adjusted odds ratio 1.71, 95% confidence interval 1.02–2.87); however, there was no difference in clinical events (a combined end point of death or nonfatal myocardial infarction) in a median follow-up of 16 months—although this study was obviously underpowered for this end point.²⁵

On the other hand, in 2438 patients with STEMI from the FAST-MI 2010 cohort (French Registry of Acute Coronary Syndrome),²⁶ morphine was not associated with higher risk of clinical events, including death (adjusted odds ratio 0.48, 95% confidence interval 0.12–1.85) and stent thrombosis (adjusted odds ratio 1.31, 95% confidence interval 0.36–4.74). The latter end point is evidently of particular interest for the issue of morphine effects on P2Y₁₂ receptor antagonist effectiveness. One-year crude mortality was lower among patients who were given morphine, although after adjustment this difference became nonsignificant (adjusted hazard ratio 0.69, 95% confidence interval 0.35–1.37; Figure 2). Of note, the same results were replicated in the FAST-MI 2005 cohort (3059 STEMI patients). In summary, according to this analysis of the FAST-MI cohorts, morphine was not associated with higher rate of clinical events or 1-year mortality in a total STEMI population of ≈ 5500 patients.

In a smaller study of 765 patients with STEMI and 993 patients with non-STEMI from the Acute Coronary Syndrome Israeli Survey 2008 database, intravenous narcotics use was not associated with 30-day mortality after propensity score matching and multivariable adjustment (odds ratio 0.40, 95% confidence interval 0.14–1.14, for STEMI and 0.56, 95% confidence interval 0.11–2.07, for non-STEMI patients). The raw mortality rate was lower among patients who received intravenous narcotics.²⁷

Mechanistic Insights

An obvious mechanism for the interaction between P2Y₁₂ receptor antagonists and morphine is the inhibition of gastric emptying, which can result in marked delays in the absorption of orally administered drugs.²⁸ This effect is important for clopidogrel, which is almost entirely absorbed in the intestine,²⁹ and the same is true for ticagrelor³⁰ and prasugrel.³¹ The emetic effect of morphine may also interfere with oral administration of antiplatelet agents, and this raises the question of whether cangrelor, a recently approved potent intravenous P2Y₁₂ receptor antagonist, would be unaffected by concurrent opioid use. On the contrary, there is also evidence that opioid agonists may be involved in favorable cardioprotective effects on the myocardium. Morphine, for example, has been shown to enhance conditioning effects in the setting of ACS³² and was associated with perioperative cardioprotection (in terms of preservation of contractile function³³ and reduced cardiac biomarker release³⁴) in patients undergoing cardiac surgery. These data suggest that from a mechanistic point of view, there is no clear-cut picture regarding the overall—beneficial or adverse—effect of morphine in ACS patients.

The mechanism underlying the effect of morphine on P2Y₁₂ receptor antagonist absorption is also relevant for the question of whether other opioid receptor agonists, including pethidine and fentanyl, have similar effects. Unfortunately, there is no sufficient evidence as to the existence and effect size of such potential interactions. One might argue that

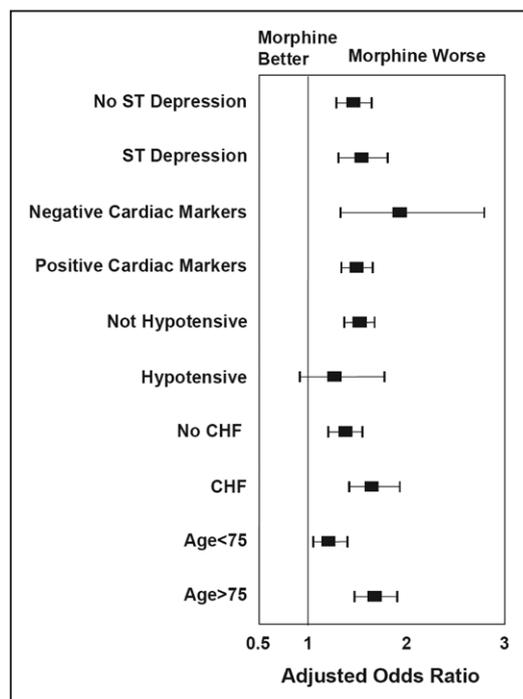


Figure 1. Adjusted odds ratios of in-hospital mortality with morphine use across subgroups in the CRUSADE registry (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines). CHF indicates chronic heart failure. Reproduced from Meine et al²⁴ with permission. Copyright ©2005, Elsevier.

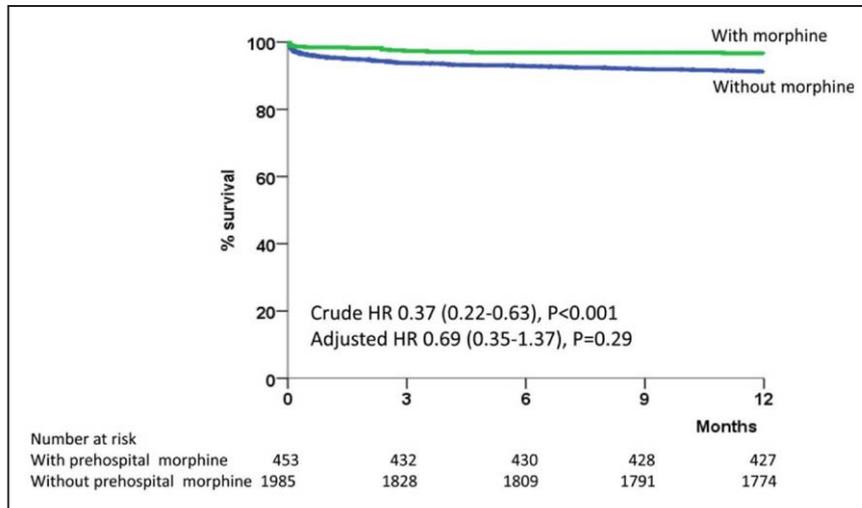


Figure 2. One-year survival according to morphine use in the FAST-MI 2010 cohort (French Registry of Acute Coronary Syndrome). HR indicates hazard ratio. Reproduced from Puymirat et al²⁶ with permission. Copyright ©2016, Oxford University Press.

because all opioids affect gut motility and increase gastrointestinal transit time, they should affect antiplatelet agent absorption in a similar way. On the other hand, existing evidence suggests that there is a differential involvement of μ -opioid receptor sites and responsible regions for the different opioid agonists, which means that they may cause reduced gastrointestinal motility through different mechanisms, and the degree of induced dysmotility may vary.³⁵ In view of the above considerations, generalization of the observations regarding morphine to all opioids should be done with some reserve—at least until more evidence becomes available.

Conclusions

The weight of existing pharmacokinetic and pharmacodynamic evidence suggests an adverse effect of morphine on platelet inhibition by P2Y₁₂ receptor antagonists, although there are some conflicting reports, especially as far as prasugrel and ticagrelor are concerned. This interaction is most possibly because of the inhibitory effect of opioids on gut motility. On the contrary, there is no definitive evidence that morphine use is associated with higher rate of hard clinical end points in the setting of current management of STEMI and non-STEMI patients treated with PCI, and the lack of randomized studies with clinical end points precludes drawing incontrovertible informed conclusions. In addition to this central unresolved issue regarding the true clinical significance of the observed interaction in terms of hard outcomes, future research should probably address other aspects of the situation as well, including the generalizability of findings regarding morphine to other opioids, the exact mechanisms underlying the observed interactions, the efficacy of potential measures that could counteract inadequate platelet inhibition resulting from these interactions (eg, novel opioid antagonists are being tested, which inhibit peripheral/gastrointestinal morphine effects, with no or minimal antagonism in the central nervous system^{36,37}), and the relative significance of these effects in different patient subgroups and clinical settings. Another question to be answered is whether there are significant differences between available P2Y₁₂ receptor antagonists, in terms of their susceptibility to be affected, pharmacodynamically or pharmacokinetically, by morphine.

In this context, erring on the side of safety seems to be the smart choice, meaning that opioids should probably not be used unless considered truly necessary in patients with ACS. In this respect, including opioid analgesia in routine prehospital or emergency room protocols for STEMI or non-STEMI patients should probably be discontinued because—until further and better evidence is available—coadministration of morphine with P2Y₁₂ receptor antagonists should be a careful benefit-over-harm ratio-considering choice.

Disclosures

None.

References

- Levine GN, Bates ER, Mauri L, Mehran R, Mukherjee D, Newby LK, Fihn SD, Fleisher LA, O'Gara PT, Granger CB, Sabatine MS, Smith PK, Lange RA, Smith SC. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [published online ahead of print March 29, 2016]. *Circulation*. 2016; doi: 10.1161/CIR.0000000000000404.
- Steg PG, James SK, Atar D, Badano LP, Lundqvist CB, Borger MA, Di Mario C, Dickstein K, Ducrocq G, Fernandez-Aviles F, Gershlick AH, Giannuzzi P, Halvorsen S, Huber K, Juni P, Kastrati A, Knuuti J, Lenzen MJ, Mahaffey KW, Valgimigli M, Van'T Hof A, Widimsky P, Zahger D. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J*. 2012;33:2569–2619.
- Roffi M, Patrono C, Collet J-P, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2015;32:2999–3054.
- Parodi G. Editor's Choice—Chest pain relief in patients with acute myocardial infarction. *Eur Heart J Acute Cardiovasc Care*. 2016;5:277–281. doi: 10.1177/2048872615584078.
- Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Jr, Ganiats TG, Holmes DR, Jr, Jaffe AS, Jneid H, Kelly RF, Kontos MC, Levine GN, Liebson PR, Mukherjee D, Peterson ED, Sabatine MS, Smalling RW, Zieman SJ; American College of Cardiology; American Heart Association Task Force on Practice Guidelines; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons; American Association for Clinical Chemistry. 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/

- American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;64:e139–e228. doi: 10.1016/j.jacc.2014.09.017.
6. Kubica J, Kubica A, Jilma B, Adamski P, Hobl EL, Navarese EP, Siller-Matula JM, Dąbrowska A, Fabiszak T, Koziński M, Gurbel PA. Impact of morphine on antiplatelet effects of oral P2Y₁₂ receptor inhibitors. *Int J Cardiol*. 2016;215:201–208. doi: 10.1016/j.ijcard.2016.04.077.
 7. Beygui F, Castren M, Brunetti ND, Rosell-Ortiz F, Christ M, Zeymer U, Huber K, Folke F, Svensson L, Bueno H, Van't Hof A, Nikolaou N, Nibbe L, Charpentier S, Swahn E, Tubaro M, Goldstein P. Pre-hospital management of patients with chest pain and/or dyspnoea of cardiac origin. A position paper of the Acute Cardiovascular Care Association (ACCA) of the ESC [published online ahead of print August 27, 2015]. *Eur Heart J Acute Cardiovasc Care*. 2015. pii: 2048872615604119.
 8. Hobl EL, Stimpfl T, Ebner J, Schoergenhofer C, Derhaschnig U, Sunder-Plassmann R, Jilma-Stohlawetz P, Mannhalter C, Posch M, Jilma B. Morphine decreases clopidogrel concentrations and effects: a randomized, double-blind, placebo-controlled trial. *J Am Coll Cardiol*. 2014;63:630–635. doi: 10.1016/j.jacc.2013.10.068.
 9. Zeymer U, Mark B, Montalescot G, Thiele H, Zahn R. Influence of morphine on the effect of clopidogrel and prasugrel in patients with ST-elevation myocardial infarction. Results of the ETAMI trial. *Eur Heart J*. 2015;36:227–228. Abstract.
 10. Parodi G, Valenti R, Bellandi B, Migliorini A, Marcucci R, Comito V, Carrabba N, Santini A, Gensini GF, Abbate R, Antoniucci D. Comparison of prasugrel and ticagrelor loading doses in ST-segment elevation myocardial infarction patients: RAPID (Rapid Activity of Platelet Inhibitor Drugs) primary PCI study. *J Am Coll Cardiol*. 2013;61:1601–1606. doi: 10.1016/j.jacc.2013.01.024.
 11. Parodi G, Bellandi B, Valenti R, Migliorini A, Marcucci R, Carrabba N, Giurlani L, Gensini GF, Abbate R, Antoniucci D. Comparison of double (360 mg) ticagrelor loading dose with standard (60 mg) prasugrel loading dose in ST-elevation myocardial infarction patients: the Rapid Activity of Platelet Inhibitor Drugs (RAPID) primary PCI 2 study. *Am Heart J*. 2014;167:909–914. doi: 10.1016/j.ahj.2014.03.011.
 12. Kubica J, Adamski P, Ostrowska M, Sikora J, Kubica JM, Sroka WD, Stankowska K, Buszko K, Navarese EP, Jilma B, Siller-Matula JM, Marszałł MP, Rośc D, Koziński M. Morphine delays and attenuates ticagrelor exposure and action in patients with myocardial infarction: the randomized, double-blind, placebo-controlled IMPRESSION trial. *Eur Heart J*. 2016;37:245–252. doi: 10.1093/eurheartj/ehv547.
 13. Silvain J, Storey RF, Cayla G, Esteve JB, Dillinger JG, Rousseau H, Tsatsaris A, Baradat C, Salhi N, Hamm CW, Lapostolle F, Lassen JF, Collet JP, Ten Berg JM, Van't Hof AW, Montalescot G. P2Y₁₂ receptor inhibition and effect of morphine in patients undergoing primary PCI for ST-segment elevation myocardial infarction. The PRIVATE-ATLANTIC study. *Thromb Haemost*. 2016;116:369–378. doi: 10.1160/TH15-12-0944.
 14. Thomas MR, Morton AC, Hossain R, Chen B, Luo L, Shahari NN, Hua P, Beniston RG, Judge HM, Storey RF. Morphine delays the onset of action of prasugrel in patients with prior history of ST-elevation myocardial infarction. *Thromb Haemost*. 2016;116:96–102. doi: 10.1160/TH16-02-0102.
 15. Johnson TW, Mumford AD, Scott LJ, Mundell S, Butler M, Strange JW, Rogers CA, Reeves BC, Baumbach A. A Study of Platelet Inhibition, Using a 'Point of Care' Platelet Function Test, following Primary Percutaneous Coronary Intervention for ST-Elevation Myocardial Infarction [PINPOINT-PPCI]. *PLoS One*. 2015;10:e0144984. doi: 10.1371/journal.pone.0144984.
 16. Rollini F, Franchi F, Hu J, Kureti M, Aggarwal N, Durairaj A, Park Y, Seawell M, Cox-Alomar P, Zenni MM, Guzman LA, Suryadevara S, Antoun P, Bass TA, Angiolillo DJ. Crushed prasugrel tablets in patients with STEMI undergoing primary percutaneous coronary intervention: the CRUSH study. *J Am Coll Cardiol*. 2016;67:1994–2004. doi: 10.1016/j.jacc.2016.02.045.
 17. Parodi G, Bellandi B, Xanthopoulos I, Capranzano P, Capodanno D, Valenti R, Stavrou K, Migliorini A, Antoniucci D, Tamburino C, Alexopoulos D. Morphine is associated with a delayed activity of oral antiplatelet agents in patients with ST-elevation acute myocardial infarction undergoing primary percutaneous coronary intervention. *Circ Cardiovasc Interv*. 2015;8:1–7. doi: 10.1161/CIRCINTERVENTIONS.114.001593.
 18. Alexopoulos D, Xanthopoulos I, Gkizas V, Kassimis G, Theodoropoulos KC, Makris G, Koutsogiannis N, Damelou A, Tsigkas G, Davlouros P, Hahalis G. Randomized assessment of ticagrelor versus prasugrel antiplatelet effects in patients with ST-segment-elevation myocardial infarction. *Circ Cardiovasc Interv*. 2012;5:797–804. doi: 10.1161/CIRCINTERVENTIONS.112.972323.
 19. Alexopoulos D, Gkizas V, Patsilinos S, Xanthopoulos I, Angelidis C, Anthopoulos P, Makris G, Perperis A, Karanikas S, Koutsogiannis N, Davlouros P, Deftereos S, Chiladakis J, Hahalis G. Double versus standard loading dose of ticagrelor: onset of antiplatelet action in patients with STEMI undergoing primary PCI. *J Am Coll Cardiol*. 2013;62:940–941. doi: 10.1016/j.jacc.2013.05.021.
 20. Xanthopoulos I, Davlouros P, Tsigkas G, Koutsogiannis N, Patsilinos S, Deftereos S, Hahalis G, Alexopoulos D. Factors affecting platelet reactivity 2 hours after P2Y₁₂ receptor antagonist loading in primary percutaneous coronary intervention for ST-elevation myocardial infarction—impact of pain-loading time. *Circ J*. 2016;80:442–449. doi: 10.1253/circj.CJ-15-0495.
 21. Hobl EL, Reiter B, Schoergenhofer C, Schwameis M, Derhaschnig U, Kubica J, Stimpfl T, Jilma B. Morphine decreases ticagrelor concentrations but not its antiplatelet effects: a randomized trial in healthy volunteers. *Eur J Clin Invest*. 2016;46:7–14. doi: 10.1111/eci.12550.
 22. Hobl EL, Reiter B, Schoergenhofer C, Schwameis M, Derhaschnig U, Lang IM, Stimpfl T, Jilma B. Morphine interaction with prasugrel: a double-blind, cross-over trial in healthy volunteers. *Clin Res Cardiol*. 2016;105:349–355. doi: 10.1007/s00392-015-0927-z.
 23. Franchi F, Rollini F, Cho JR, Bhatti M, DeGroat C, Ferrante E, Dunn EC, Nanavati A, Carraway E, Suryadevara S, Zenni MM, Guzman LA, Bass TA, Angiolillo DJ. Impact of Escalating Loading Dose Regimens of Ticagrelor in Patients With ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention: Results of a Prospective Randomized Pharmacokinetic and Pharmacodynamic Investigation. *JACC Cardiovasc Interv*. 2015;8:1457–1467. doi: 10.1016/j.jcin.2015.02.030.
 24. Meine TJ, Roe MT, Chen AY, Patel MR, Washam JB, Ohman EM, Peacock WF, Pollack CV, Jr, Gibler WB, Peterson ED; CRUSADE Investigators. Association of intravenous morphine use and outcomes in acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative. *Am Heart J*. 2005;149:1043–1049. doi: 10.1016/j.ahj.2005.02.010.
 25. de Waha S, Eitel I, Desch S, Fuernau G, Lurz P, Urban D, Schuler G, Thiele H. Intravenous morphine administration and reperfusion success in ST-elevation myocardial infarction: insights from cardiac magnetic resonance imaging. *Clin Res Cardiol*. 2015;104:727–734. doi: 10.1007/s00392-015-0835-2.
 26. Puymirat E, Lamhaut L, Bonnet N, Aissaoui N, Henry P, Cayla G, Cattan S, Steg G, Mock L, Ducrocq G, Goldstein P, Schiele F, Bonnefoy-Cudraz E, Simon T, Danchin N. Correlates of pre-hospital morphine use in ST-elevation myocardial infarction patients and its association with in-hospital outcomes and long-term mortality: the FAST-MI (French Registry of Acute ST-elevation and non-ST-elevation Myocardial Infarction) programme. *Eur Heart J*. 2016;37:1063–1071. doi: 10.1093/eurheartj/ehv567.
 27. Iakobishvili Z, Porter A, Battler A, Behar S, Roth A, Atar S, Boyko V, Mager A, Hasdai D. Effect of narcotic treatment on outcomes of acute coronary syndromes. *Am J Cardiol*. 2010;105:912–916. doi: 10.1016/j.amjcard.2009.11.027.
 28. Nimmo WS, Heading RC, Wilson J, Tohill P, Prescott LF. Inhibition of gastric emptying and drug absorption by narcotic analgesics. *Br J Clin Pharmacol*. 1975;2:509–513.
 29. Lins R, Broekhuysen J, Necciari J, Deroubaix X. Pharmacokinetic profile of 14C-labeled clopidogrel. *Semin Thromb Hemost*. 1999;25(suppl 2):29–33.
 30. Teng R, Oliver S, Hayes MA, Butler K. Absorption, distribution, metabolism, and excretion of ticagrelor in healthy subjects. *Drug Metab Dispos*. 2010;38:1514–1521. doi: 10.1124/dmd.110.032250.
 31. Farid NA, Smith RL, Gillespie TA, Rash TJ, Blair PE, Kurihara A, Goldberg MJ. The disposition of prasugrel, a novel thienopyridine, in humans. *Drug Metab Dispos*. 2007;35:1096–1104. doi: 10.1124/dmd.106.014522.
 32. Rentoukas I, Giannopoulos G, Kaoukis A, Kossyvakis C, Raisakis K, Driva M, Panagopoulou V, Tsarouchas K, Vavetsi S, Pyrgakis V, Deftereos S. Cardioprotective role of remote ischemic preconditioning in primary percutaneous coronary intervention: enhancement by opioid action. *JACC Cardiovasc Interv*. 2010;3:49–55. doi: 10.1016/j.jcin.2009.10.015.
 33. Murphy GS, Szokol JW, Marymont JH, Avram MJ, Vender JS. Opioids and cardioprotection: the impact of morphine and fentanyl on recovery

- of ventricular function after cardiopulmonary bypass. *J Cardiothorac Vasc Anesth.* 2006;20:493–502. doi: 10.1053/j.jvca.2005.07.036.
34. Zhang R, Shen L, Xie Y, Gen L, Li X, Ji Q. Effect of morphine-induced postconditioning in corrections of tetralogy of fallot. *J Cardiothorac Surg.* 2013;8:76. doi: 10.1186/1749-8090-8-76.
35. Mori T, Shibasaki Y, Matsumoto K, Shibasaki M, Hasegawa M, Wang E, Masukawa D, Yoshizawa K, Horie S, Suzuki T. Mechanisms that underlie μ -opioid receptor agonist-induced constipation: differential involvement of μ -opioid receptor sites and responsible regions. *J Pharmacol Exp Ther.* 2013;347:91–99. doi: 10.1124/jpet.113.204313.
36. Eldon MA, Kugler AR, Medve RA, Bui K, Butler K, Sostek M. Safety, tolerability, pharmacokinetics, and pharmacodynamic effects of naloxegol at peripheral and central nervous system receptors in healthy male subjects: A single ascending-dose study. *Clin Pharmacol Drug Dev.* 2015;4:434–441. doi: 10.1002/cpdd.206.
37. Yancey-Wrona J, Dallaire B, Bilsky E, Bath B, Burkart J, Webster L, Magiera D, Yang X, Phelps M, Sadee W. 6β -naltrexol, a peripherally selective opioid antagonist that inhibits morphine-induced slowing of gastrointestinal transit: an exploratory study. *Pain Med.* 2011;12:1727–1737. doi: 10.1111/j.1526-4637.2011.01279.x.

P2Y₁₂ Receptor Antagonists and Morphine: A Dangerous Liaison?
Georgios Giannopoulos, Spyridon Deftereos, Fotios Kolokathis, Ioanna Xanthopoulou, John
Lekakis and Dimitrios Alexopoulos

Circ Cardiovasc Interv. 2016;9:

doi: 10.1161/CIRCINTERVENTIONS.116.004229

Circulation: Cardiovascular Interventions is published by the American Heart Association, 7272 Greenville
Avenue, Dallas, TX 75231

Copyright © 2016 American Heart Association, Inc. All rights reserved.

Print ISSN: 1941-7640. Online ISSN: 1941-7632

The online version of this article, along with updated information and services, is located on the
World Wide Web at:

<http://circinterventions.ahajournals.org/content/9/9/e004229>

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation: Cardiovascular Interventions* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

Reprints: Information about reprints can be found online at:
<http://www.lww.com/reprints>

Subscriptions: Information about subscribing to *Circulation: Cardiovascular Interventions* is online at:
<http://circinterventions.ahajournals.org/subscriptions/>