

# Morphine and Cardiovascular Outcomes Among Patients With Non-ST-Segment Elevation Acute Coronary Syndromes Undergoing Coronary Angiography



Remo H.M. Furtado, MD, PhD,<sup>a,b</sup> José C. Nicolau, MD, PhD,<sup>b</sup> Jianping Guo, MAS,<sup>a</sup> Kyungah Im, PhD,<sup>a</sup> Jennifer A. White, MS,<sup>c</sup> Marc S. Sabatine, MD, MPH,<sup>a</sup> L. Kristin Newby, MD, MHS,<sup>c</sup> Robert P. Giugliano, MD, SM<sup>a</sup>

## ABSTRACT

**BACKGROUND** Mechanistic studies have shown that morphine blunts the antiplatelet effects of oral adenosine diphosphate receptor blockers. However, the clinical relevance of this interaction is controversial.

**OBJECTIVES** This study sought to explore the association between morphine and ischemic events in 5,438 patients treated with concomitant clopidogrel presenting with non-ST-segment elevation acute coronary syndromes (NSTEMI) in the EARLY ACS (Early Glycoprotein IIb/IIIa Inhibition in Patients With Non-ST-Segment Elevation Acute Coronary Syndrome) trial. Patients not treated with clopidogrel (n = 3,462) were used as negative controls.

**METHODS** Endpoints were the composite of death, myocardial infarction (MI), recurrent ischemia, or thrombotic bailout at 96 h (4-way endpoint) and the composite of death or MI at 30 days.

**RESULTS** In patients treated with clopidogrel, morphine use was associated with higher rates of the 4-way endpoint at 96 h (adjusted odds ratio [OR]: 1.40; 95% confidence interval [CI]: 1.04 to 1.87; p = 0.026). There was a trend for higher rates of death or MI at 30 days (adjusted OR: 1.29; 95% CI: 0.98 to 1.70; p = 0.072), driven by events in the first 48 h (adjusted hazard ratio: 1.54; 95% CI: 1.07 to 2.23; p = 0.021). In patients not treated with clopidogrel, morphine was not associated with either the 4-way endpoint at 96 h (adjusted OR: 1.05; 95% CI: 0.74 to 1.49; p = 0.79; p<sub>interaction</sub> = 0.36) or death or MI at 30 days (adjusted OR: 1.07; 95% CI: 0.77 to 1.48; p = 0.70; p<sub>interaction</sub> = 0.46).

**CONCLUSIONS** When used concomitantly with clopidogrel pre-treatment, morphine was associated with higher rates of ischemic events in patients with NSTEMI. (EARLY ACS: Early Glycoprotein IIb/IIIa Inhibition in Patients With Non-ST-Segment Elevation Acute Coronary Syndrome; [NCT00089895](https://doi.org/10.1016/j.jacc.2019.11.035)) (J Am Coll Cardiol 2020;75:289-300)  
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From the <sup>a</sup>Thrombosis In Myocardial Infarction Study Group-Brigham and Women's Hospital, Boston, Massachusetts; <sup>b</sup>Instituto do Coracao (InCor), Hospital das Clinicas da Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil; and the <sup>c</sup>Duke Clinical Research Institute, Durham, North Carolina. The EARLY ACS trial received grant funding from Schering-Plough. The work of Dr. Furtado was supported by the Lemann Foundation Cardiovascular Research Postdoctoral Fellowship, Harvard University/Brigham and Women's Hospital. The current analyses received no sources of external funding. Dr. Furtado has received honoraria from AstraZeneca; and has received research grants from AstraZeneca, DalCor, Boehringer Ingelheim, Pfizer, Bayer, and Sanofi. Dr. Nicolau has received research grants from Amgen Inc., Bayer Healthcare Pharmaceuticals, Bristol-Myers Squibb Company, CLS Behring, DalCor, Janssen Pharmaceuticals Inc., Novartis, Population Research Institute, Novo Nordisk, Sanofi, and AstraZeneca; and has served as a consultant/on the advisory board for Bayer, Daiichi-Sankyo, Novartis, Servier, and Sanofi. Dr. Guo has received research grants from Merck. Dr. Im has received research grants from Merck; and is a member of the Thrombosis In Myocardial Infarction Study Group, which has received institutional research grant support through Brigham and Women's Hospital from Abbott, Amgen, Aralex, AstraZeneca, Bayer HealthCare Pharmaceuticals Inc., BRAHMS, Daiichi-Sankyo, Eisai, GlaxoSmithKline, Intarcia, Janssen, MedImmune, Merck, Novartis, Pfizer, Poxel, Quark Pharmaceuticals, Roche, Takeda, The Medicines Company, and Zora Biosciences. Dr. Sabatine has received research grant support through Brigham and Women's Hospital from Abbott Laboratories, Amgen, AstraZeneca, Bayer, Daiichi-Sankyo, Eisai, Gilead, GlaxoSmithKline, Intarcia, Janssen Research and Development, The Medicines Company, MedImmune, Merck, Novartis, Poxel, Pfizer, Quark Pharmaceuticals, Roche Diagnostics, and Takeda; is a member of the Thrombosis In Myocardial Infarction Study Group, which has also received institutional research

**ABBREVIATIONS  
AND ACRONYMS****ACS** = acute coronary syndromes**ADP** = adenosine diphosphate**CI** = confidence interval**FDA** = U.S. Food and Drug Administration**IPTW** = inverse probability of treatment weighting**MI** = myocardial infarction**NSTEACS** = non-ST-segment elevation acute coronary syndromes**OR** = odds ratio**STEMI** = ST-segment elevation myocardial infarction**TIMI** = Thrombolysis In Myocardial Infarction

Morphine has been recommended for management of acute chest pain in patients with acute coronary syndromes (ACS) since the beginning of the 20th century (1). Currently, morphine is endorsed by all guidelines for the management of pain in patients with non-ST-segment elevation acute coronary syndromes (NSTEACS), although no randomized trial has been conducted so far to assess its clinical safety (2,3).

From a pharmacological perspective, morphine and other opioids can delay absorption and blunt the antiplatelet effect of oral adenosine diphosphate (ADP) receptor blockers. In a randomized, placebo-controlled trial in 24 healthy volunteers, Hobl et al. (4) showed that concomitant morphine reduced active metabolite exposure and antiplatelet effects after a loading dose of 600 mg clopidogrel. This interaction was also shown subsequently for prasugrel and ticagrelor in stable patients post-ACS (5), in acute myocardial infarction (MI) (6–9), and during elective percutaneous coronary intervention (10). These data led the U.S. Food and Drug Administration (FDA) in 2018 to update the labels of all 3 widely used oral ADP blockers (clopidogrel, prasugrel, and ticagrelor) to include a warning about drug interaction with morphine and other opioids (11–13).

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The clinical relevance of those pharmacological findings is still a matter of debate. In the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress ADverse Outcomes with Early Implementation of the ACC/AHA Guidelines) registry, morphine use in the first 24 h of hospital admission was associated with higher mortality and recurrent MI in individuals with NSTEACS (14). On the other hand, a subanalysis from the FAST-MI (French Registry of Acute ST-elevation and non-ST

elevation Myocardial Infarction) registry did not find any association between the composite of death or MI and pre-hospital morphine use in patients with ST-segment elevation myocardial infarction (STEMI) (15). Other reports in ACS have also found conflicting results (16–19).

The benefit of clopidogrel in patients with NSTEACS has been described previously (20,21). Therefore, on the basis of the aggregate data from the aforementioned pharmacological studies, our main objective was to test the hypothesis that morphine use is associated with higher risk of cardiac ischemic events in patients being administered concomitant clopidogrel for ACS. Moreover, if a possible higher risk with intravenous morphine was indeed explained by impairment of clopidogrel absorption and a decrease in its antiplatelet effect, we would not expect to see any increase in risk in those patients taking morphine without concomitant clopidogrel, nor any increase in risk of late events.

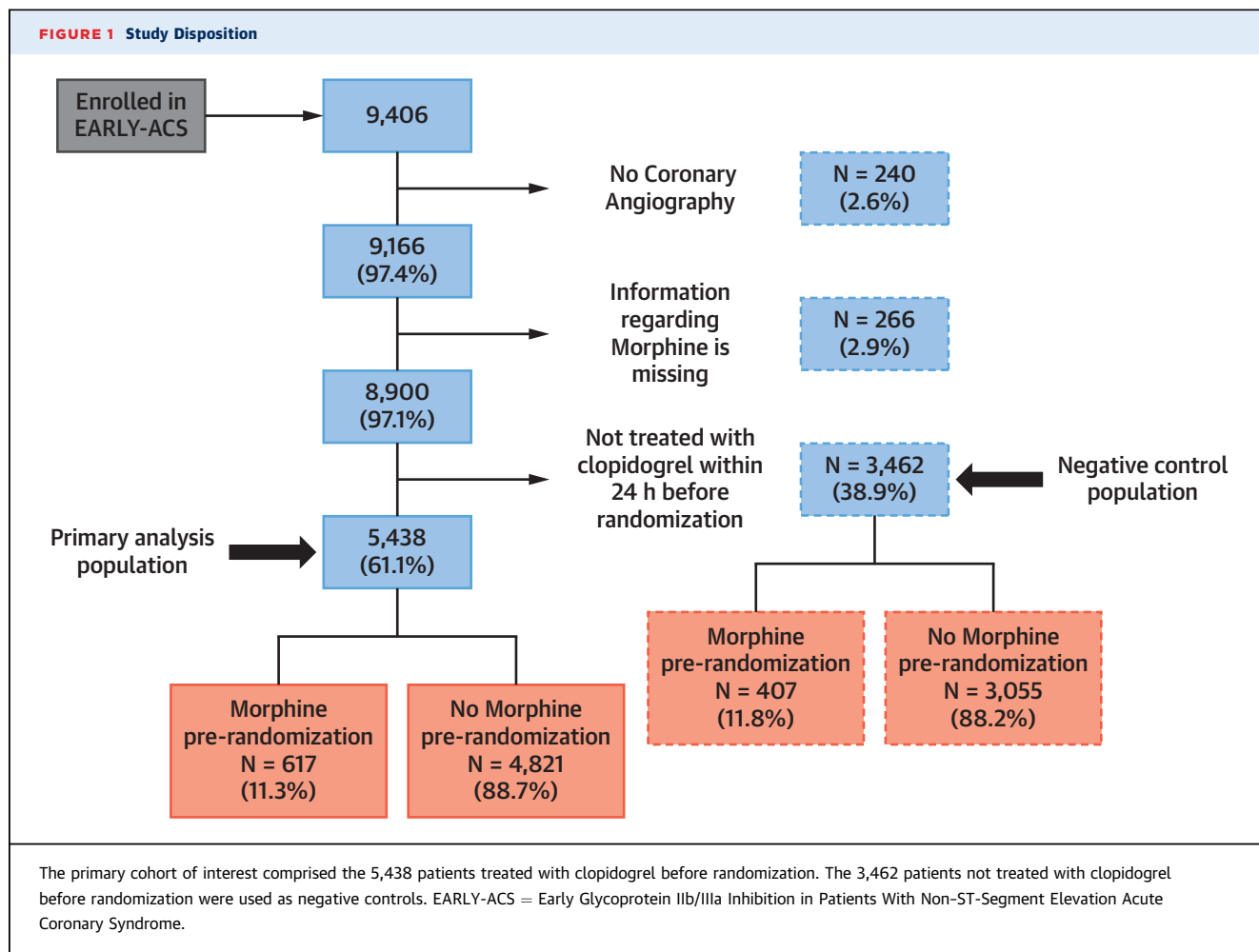
**METHODS**

**POPULATION AND ENDPOINT SELECTION.** This was a post hoc subanalysis from the EARLY ACS trial, which randomly assigned high-risk patients with NSTEACS to early (i.e., before coronary angiography) versus delayed, provisional (during or soon after percutaneous coronary intervention) use of the intravenous glycoprotein IIb/IIIa antagonist eptifibatide. The trial design and main results were published previously (22,23). Briefly, eligible patients had NSTEACS presenting in the first 24 h after symptom onset with at least 2 of the following high-risk features: ST-segment deviation, increased troponin, or age of  $\geq 60$  years. The time from hospital presentation to enrollment was no more than 12 h. All patients planned to undergo an invasive management, and randomization took place before cardiac angiography. Invasive procedures were to be performed at least 12 h after the study drug was started.

Randomization was stratified according to intention to use upstream clopidogrel before coronary

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angiography. Information regarding clopidogrel use within 24 h before randomization was prospectively reported by the investigators. Intravenous morphine use was also reported by the investigators in a dedicated field on the study case report form as occurring within 7 days before randomization or not.

Because the aforementioned concerns with morphine were related to its potential interaction with ADP receptor blockers, our primary population of interest comprised those patients who were treated with clopidogrel within 24 h before randomization. We evaluated the primary composite of death, nonfatal MI, recurrent ischemia with need for urgent revascularization, or thrombotic bailout at 96 h and key secondary endpoint (death or MI at 30 days) as defined in the main trial ([Online Appendix](#)). We also analyzed bleeding per Thrombolysis In Myocardial Infarction (TIMI) criteria at 120 h. Additionally, we analyzed death or MI at 96 h and bleeding per TIMI criteria at 96 h as exploratory endpoints. All study efficacy endpoints were assessed by an independent

adjudication committee, which was kept blinded to the trial randomized treatment but not blinded to morphine or clopidogrel use.

**STATISTICAL ANALYSIS.** Categorical variables were compared with chi-square or Fisher exact tests, and continuous variables were compared with 2-sample Student's *t*-test or Wilcoxon test, as appropriate.

Outcomes of interest (ischemic and bleeding endpoints and serious adverse events) were defined primarily as binary endpoints because of the relatively short follow-up time, but later we also derived the time-to-event endpoint for the landmark analysis. For our primary findings, all modeling was done by unweighted and weighted logistic regression models. Results are summarized as odds ratios (ORs) with corresponding 95% confidence intervals (CIs).

We developed a propensity score model for morphine use. The score was built from a logistic regression model, taking into account all variables with significant ( $p < 0.05$ ) differences or  $>10\%$

**TABLE 1** Baseline Characteristics According to Morphine Administration Before Randomization Among Patients Pre-Treated With Clopidogrel (n = 5,438)

	Morphine (n = 617, 11.3%)	No Morphine (n = 4,821, 88.7%)	p Value	Standardized Difference, %
Age, yrs	66.1 (59.0-73.3)	67.2 (59.7-74.6)	0.093	-5.40
Female	169 (27.39)	1,525 (31.63)	0.032	-9.31
BMI, kg/m <sup>2</sup>	27.8 (25.1-31.1)	27.1 (24.6-30.1)	<0.001	13.82
Weight <60 kg	38 (6.2)	406 (8.4)	0.053	-8.71
Systolic blood pressure	141 (127-160)	142 (129-160)	0.34	-3.49
Diastolic blood pressure	80 (70-90)	80 (70-90)	0.33	-5.98
Heart rate	76 (65-88)	76 (66-88)	0.28	-0.32
Estimated creatinine clearance <50 ml/min	89 (14.7)	829 (17.8)	0.054	-8.56
Hypertension	462 (74.9)	3,363 (69.8)	0.009	11.46
Dyslipidemia	372 (60.4)	2,695 (55.9)	0.034	9.11
Heart failure	98 (15.9)	581 (12.1)	0.007	11.01
Diabetes mellitus	202 (32.7)	1,403 (29.1)	0.062	7.88
Prior CAD	218 (35.4)	1,448 (30.1)	0.007	11.40
Previous myocardial infarction	205 (33.2)	1,343 (27.9)	0.006	11.66
Previous PCI	188 (30.5)	1,244 (25.8)	0.013	10.38
Previous CABG	105 (17.0)	601 (12.5)	0.002	12.86
Prior stroke	32 (5.2)	235 (4.9)	0.74	1.40
PAD	79 (13.1)	462 (9.7)	0.009	10.74
Current smoker	194 (31.4)	1,249 (25.9)	0.004	12.21
LVEF ≥50%	310 (65.8)	2,619 (69.8)	0.22	-8.46
North America	198 (32.1)	884 (18.3)	<0.001	32.08
Western Europe	313 (50.7)	2,425 (50.3)	<0.001	0.86
Eastern Europe	32 (5.2)	571 (11.8)	<0.001	-24.02
Middle East, Africa, or Asia-Pacific	74 (12.0)	941 (19.5)	<0.001	-20.77
Killip class II, III, or IV	88 (14.5)	464 (9.7)	<0.001	14.74
TIMI risk score	4.0 (3.0-5.0)	4.0 (3.0-5.0)	<0.001	16.92
High-risk TIMI score of 5-7	254 (42.1)	1,676 (35.6)	0.006	13.33
Transient ST-segment elevation ≥1 mm	68 (11.0)	356 (7.4)	0.002	12.61
Transient ST-segment depression ≥1 mm	241 (39.1)	2,090 (43.4)	0.043	-8.73
2 or more ischemic episodes in the last 24 h	331 (53.7)	2,631 (54.6)	0.65	-1.93
Time from onset of symptoms to randomization, h	10.4 (7.3-14.0)	10.9 (7.4-15.5)	0.043	-6.97
Time from onset of symptoms to hospitalization, h	2.4 (1.0-5.5)	3.6 (1.6-8.5)	<0.001	-11.13
Elevated troponin at admission	522 (87.4)	3,923 (83.9)	0.024	10.21

Values are median (interquartile range) or n (%), unless otherwise indicated.  
 BMI = body mass index; CABG = coronary artery bypass grafting; CAD = coronary artery disease; LVEF = left ventricle ejection fraction; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction.

standardized differences between the groups of interest (morphine vs. no morphine). In addition, the risk factors that were significantly associated with the outcome of interest at univariate analysis were also included in the propensity score model.

Missing data at baseline were infrequent (<3% for most variables). However, for creatinine and ejection fraction at baseline, data were missing in >3% of patients (3.5% for the former and 21.5% for the latter). Because these were of clinical interest in conjunction with morphine use, a multiple imputation approach was taken to fill all missing baseline characteristics before generating propensity score models. Each type of analysis was performed in each imputed dataset and then combined according to Rubin's rule (24).

In the model for the ischemic outcomes, 37 variables were used, and 37 were used for the bleeding outcomes (Online Table 1). Standardized differences before and after inverse probability of treatment weighting (IPTW) adjustment were examined graphically. A standardized difference of <10% was considered to be an acceptable balance of measured baseline characteristics by morphine use (25).

Additional sensitivity analyses were performed to test the plausibility of the association. First, patients not pre-treated with clopidogrel in the 24 h before randomization were used as negative controls, and the same endpoints were compared between morphine groups. Second, we performed a landmark

**TABLE 2** Concomitant Treatments and Angiographic Characteristics According to Morphine Administration Before Randomization

	Morphine (n = 617, 11.3%)	No Morphine (n = 4,821, 88.7%)	p Value	Standardized Difference, %
Clopidogrel loading dose, mg				
<300	61 (9.9)	435 (9.0)	0.65	2.95
≥300 and <600	378 (61.3)	3,053 (63.3)	0.65	-4.26
≥600	106 (17.2)	756 (15.7)	0.65	4.04
N/A	72 (11.7)	577 (12.0)	0.65	-0.93
Early eptifibatide randomized arm	315 (51.1)	2,425 (50.3)	0.72	1.51
PCI active or bailout kit administered	149 (24.2)	896 (18.6)	0.001	13.6
Aspirin	599 (97.1)	4,658 (96.6)	0.55	2.66
Unfractionated heparin only	238 (38.6)	1,420 (29.5)	<0.001	19.34
Low-molecular-weight heparin only	280 (45.4)	2,755 (57.2)	<0.001	-23.70
Both unfractionated and low-molecular-weight heparin	75 (12.2)	377 (7.8)	<0.001	14.50
Neither unfractionated nor low-molecular-weight heparin	24 (3.9)	269 (5.6)	<0.001	-7.96
Beta-blocker during index hospitalization	542 (87.8)	4,256 (88.3)	0.75	-1.34
ACE inhibitor during index hospitalization	411 (66.6)	3,400 (70.5)	0.046	-8.43
ARB during index hospitalization	72 (11.7)	485 (10.1)	0.21	5.17
Statin during index hospitalization	524 (84.9)	4,277 (88.7)	0.006	-11.22
PPI during index hospitalization	335 (54.3)	2,677 (55.6)	0.56	-2.48
Nitrate taken within 7 days pre-randomization	424 (68.8)	1,726 (36.0)	<0.001	69.70
Nitrate given during index hospitalization	371 (60.1)	2,821 (58.5)	0.44	3.29
PCI for index event	401 (65.0)	3,018 (62.6)	0.42	4.98
CABG for index event	64 (10.4)	566 (11.7)	0.32	-4.36
Medical management only	156 (25.3)	1,263 (26.2)	0.42	-2.09
Multivessel disease	175 (28.6)	1,538 (32.4)	0.055	-8.41
Left main coronary artery disease	55 (9.1)	446 (9.4)	0.83	-0.93
Access site femoral	491 (79.6)	4,023 (83.5)	0.016	-9.98
Access site radial or others	126 (20.4)	798 (16.6)	0.016	9.98

Values are n (%), unless otherwise indicated.  
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; N/A = not applicable (i.e., clopidogrel loading dose was not available, not given, or unknown);  
PPI = proton pump inhibitor; other abbreviations as in [Table 1](#).

analysis for death or MI at 30 days, excluding those events occurring in the first 48 h. Finally, we also compared serious adverse event rates at 30 days in the morphine versus no morphine groups. This approach was used because adverse events would not be expected to be related to a pharmacokinetic interaction between morphine and clopidogrel. Thus, we sought to rule out confounding by indication effect (that is, sicker patients more frequently being administered morphine) (26). For the landmark analysis, we used a multivariable Cox proportional hazards model to derive hazard ratios and CI. Schoenfeld residuals confirmed the proportional hazards assumption.

All tests were 2-sided, and a p value <0.05 was considered statistically significant. No adjustment for multiplicity was performed. The statistical programs used for the analysis were SAS, version 9.3 (SAS Institute Inc., Cary, North Carolina), and R, version 3.4.3 (R Core Team, Vienna, Austria).

**COMPLIANCE WITH ETHICAL STANDARDS.** This trial conformed to the recommendations of the Declaration of Helsinki and Good Clinical Practice

norms on medical research in humans. The study protocol was approved by all institutional review boards of participating sites before enrollment began. All patients signed informed consent forms before participation.

## RESULTS

**DESCRIPTIVE STATISTICS.** The EARLY ACS trial enrolled 9,406 patients ([Figure 1](#)). We excluded the 240 patients who did not undergo catheterization, leaving 9,166 individuals eligible for this analysis. Among them, 8,900 had information regarding use of morphine before randomization, and 5,438 individuals received clopidogrel within 24 h before randomization, which was our population of interest. Of these 5,438 patients, 3,927 (72.2%) were treated with <600 mg clopidogrel loading dose, 862 (15.9%) were treated with 600 mg or more, and the remaining 649 (11.9%) had no available information about the clopidogrel loading dose. Among them, 617 (11.3%) patients were administered morphine before randomization, and 4,821 (88.7%) were not.

**TABLE 3 Study Outcomes According to Morphine Use Before Randomization in Patients Pre-Treated With Clopidogrel (Unadjusted, IPTW, and Adjusted Multivariable Analysis)**

	Morphine (n = 617)	No Morphine (n = 4,821)	Unadjusted Analysis		IPTW Analysis		Adjusted Multivariable Analysis	
			Adj OR (95% CI)	p Value	Adj OR (95% CI)	p Value	Adj OR (95% CI)	p Value
Death, MI, RIUR, or TBO at 96 h	66 (10.7)	411 (8.5)	1.29 (0.98–1.69)	0.073	1.40 (1.04–1.87)	0.026	1.37 (1.02–1.84)	0.039
Death or MI at 30 days	76 (12.3)	500 (10.4)	1.21 (0.94–1.57)	0.14	1.29 (0.98–1.70)	0.072	1.26 (0.95–1.67)	0.11
TIMI major or minor bleeding at 120 h	21 (3.4)	182 (3.8)	0.90 (0.57–1.42)	0.65	0.96 (0.59–1.57)	0.89	0.93 (0.56–1.55)	0.79

Values are n (%), unless otherwise indicated.

CI = confidence interval; IPTW = inverse probability of treatment weighting; MI = myocardial infarction; Adj OR = adjusted odds ratio; RIUR = recurrent ischemia with urgent revascularization; TBO = thrombotic bailout; TIMI = Thrombolysis In Myocardial Infarction.

There were 3,462 patients who were not pre-treated with clopidogrel in the 24 h before randomization (negative control), among whom 407 (11.8%) were administered morphine before randomization, and 3,055 (88.2%) were not.

In the primary analysis population, baseline characteristics and concomitant treatments differed between the morphine groups. Among other differences, patients treated with morphine were more likely to have been enrolled in North America and more commonly had a history of previous heart failure or MI. Also, they were more likely to be in Killip class >1 and were more commonly treated with nitrates before randomization. Median time from symptom onset to hospital presentation was lower in those individuals treated with morphine (Tables 1 and 2).

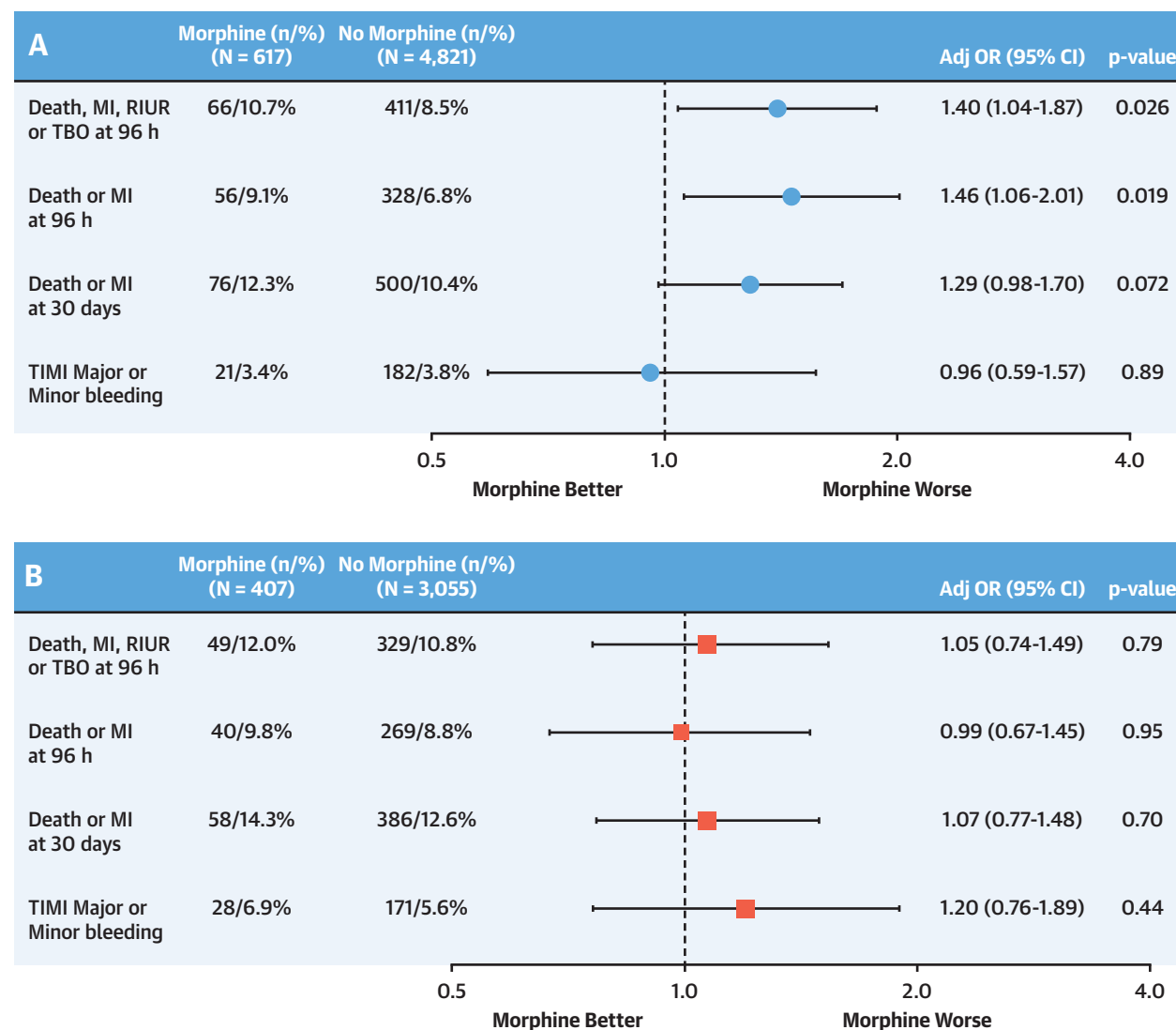
**OUTCOMES ACCORDING TO MORPHINE USE.** After IPTW adjustment, both groups were well balanced in terms of baseline characteristics, with no standardized difference above 10% in any of those parameters (Online Figures 1 and 2). With the IPTW propensity scores approach, morphine use before randomization was associated with higher rates of death, MI, thrombotic bailout, or recurrent ischemia with urgent revascularization at 96 h (adjusted OR: 1.40; 95% CI: 1.04 to 1.87;  $p = 0.026$ ) but did not increase the risk of TIMI major or minor bleeding at 120 h (adjusted OR: 0.96; 95% CI: 0.59 to 1.57;  $p = 0.89$ ). In addition, there was a trend for increase in death or MI at 30 days (adjusted OR: 1.29; 95% CI: 0.98 to 1.70;  $p = 0.072$ ). Results were similar for the exploratory endpoints of death or MI and for thrombolysis in MI (TIMI) major or minor bleeding at 96 h (adjusted OR: 1.46; 95% CI: 1.06 to 2.01;  $p = 0.019$ ; and adjusted OR: 0.91; 95% CI: 0.55 to 1.52;  $p = 0.73$ , respectively). This association was mostly driven by higher rates of MI, specifically periprocedural MI (Online Table 2). These results are summarized in Table 3, Figure 2,

and Online Figure 3. Results were similar for the primary outcome when stratified according to early versus delayed eptifibatide ( $p_{\text{interaction}} = 0.71$ ) (Online Figure 4).

**OUTCOMES ACCORDING TO MORPHINE USE—ADJUSTED MULTIVARIABLE REGRESSION APPROACH.** In the multivariable logistic regression model, similar to the IPTW adjusted model, morphine before randomization was also associated with higher risk of the primary endpoint at 96 h (adjusted OR: 1.37; 95% CI: 1.02 to 1.84;  $p = 0.039$ ). There was also a numerically higher risk of death or MI at 30 days (adjusted OR: 1.26; 95% CI: 0.95 to 1.67;  $p = 0.11$ ). Furthermore, there was no difference in TIMI major or minor bleeding at 120 h according to morphine group (adjusted OR: 0.93; 95% CI: 0.56 to 1.55;  $p = 0.79$ ) (Table 3).

**OUTCOMES AND MORPHINE USE IN PATIENTS NOT PRE-TREATED WITH CLOPIDOGREL (NEGATIVE CONTROL).** Among the 3,462 patients not administered clopidogrel within the last 24 h before randomization, those receiving morphine were more likely to have been enrolled in North America, to be in Killip class >1, and to be taking nitrates before randomization (Online Tables 3 and 4). Morphine administration was not associated with higher rates of the primary endpoint at 96 h using IPTW (adjusted OR: 1.05; 95% CI: 0.74 to 1.49;  $p = 0.79$ ) or by logistic regression (adjusted OR: 1.07; 95% CI: 0.75 to 1.51;  $p = 0.71$ ) in patients not pre-treated with clopidogrel ( $p_{\text{interaction}} = 0.36$ ); nor was morphine use in this subpopulation associated with death or MI at 30 days (adjusted OR: 1.07; 95% CI: 0.77 to 1.48;  $p = 0.70$ ; and adjusted OR: 1.06; 95% CI: 0.76 to 1.47;  $p = 0.73$ , for IPTW and logistic regression adjusted models, respectively;  $p_{\text{interaction}} = 0.46$ ). Similarly, there were no increases in risk with morphine in bleeding at 120 h (adjusted OR: 1.20; 95% CI: 0.76 to 1.89;  $p = 0.44$ ; and adjusted OR: 1.36; 95% CI: 0.85 to 2.18;  $p = 0.20$ ,

**FIGURE 2** Ischemic (at 96 h and at 30 days) and TIMI Major or Minor Bleeding (at 120 h) Endpoints According to Clopidogrel Administration at Admission Before Randomization



(A) Patients treated with concomitant clopidogrel (N = 5,438). (B) Patients not receiving clopidogrel (N = 3,462). CI = confidence interval; MI = myocardial infarction; OR = odds ratio; RIUR = recurrent ischemia with urgent revascularization; TBO = thrombotic bailout; TIMI = Thrombolysis In Myocardial Infarction.

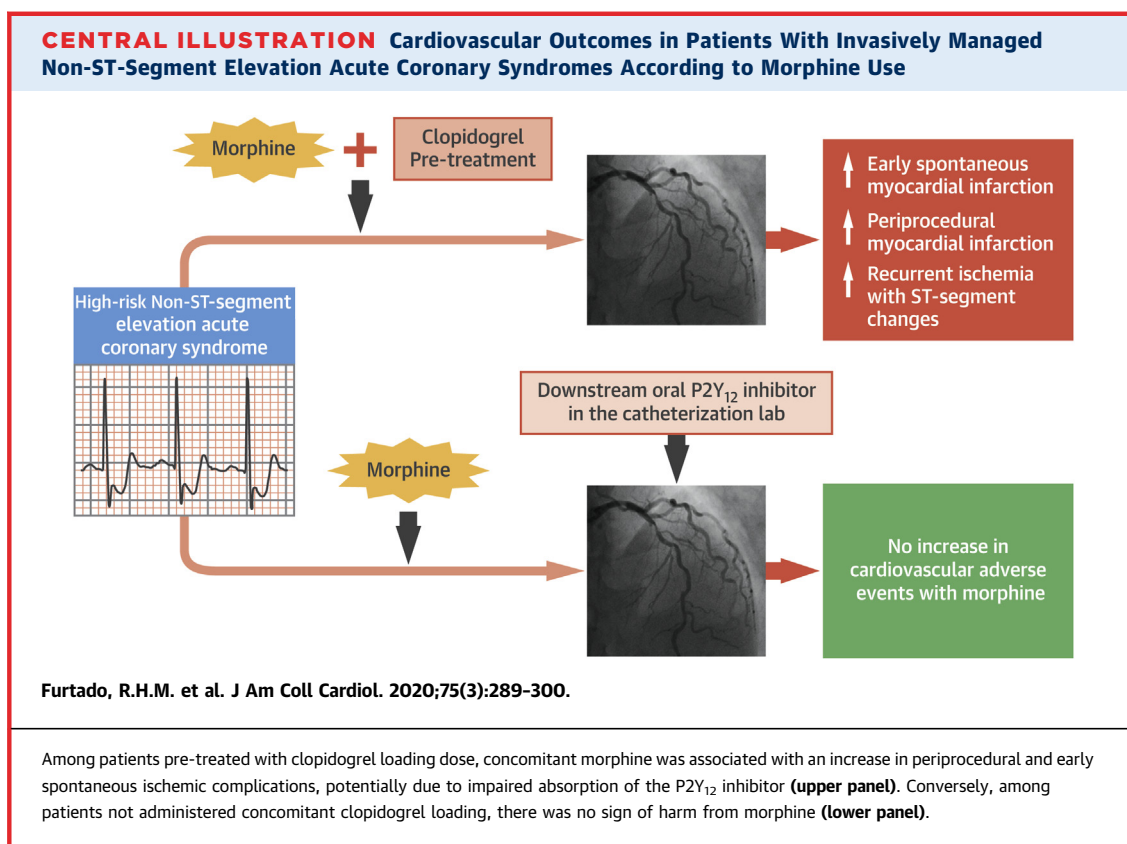
for IPTW and logistic regression adjusted models, respectively;  $p_{\text{interaction}} = 0.61$ ) (Online Table 5, Central Illustration).

**LANDMARK AND NONCARDIOVASCULAR EVENTS ANALYSES.** When only events occurring in the first 48 h were considered, there was an even stronger association of morphine use with higher rates of death or MI in patients pre-treated with clopidogrel (adjusted hazard ratio: 1.54; 95% CI: 1.07 to 2.23;  $p = 0.021$ ). Conversely, after excluding events in the

first 48 h, there was no longer a difference in rates of death or MI between both morphine groups among patients taking concomitant clopidogrel (adjusted hazard ratio: 1.00; 95% CI: 0.67 to 1.49;  $p = 0.99$ ). Among patients not taking concomitant clopidogrel, there was no association with higher event rates either at 48 h or after this time point. These results are summarized in Figure 3.

There were 221 noncardiovascular serious adverse events at 30 days in patients pre-treated with clopidogrel. There was no difference in risks of those





events with morphine use before randomization (unadjusted OR: 0.95; 95% CI: 0.62 to 1.46;  $p = 0.82$ ; IPTW-adjusted OR: 0.95; 95% CI: 0.60 to 1.51;  $p = 0.83$ ; and logistic regression-adjusted OR: 0.94; 95% CI: 0.59 to 1.49;  $p = 0.78$ ).

## DISCUSSION

**STUDY MAIN FINDINGS.** We have observed that morphine used concomitantly with clopidogrel pre-treatment was associated with higher short-term risk of acute ischemic events among patients with invasively managed NSTEMI/UA. Based on our results, it seems reasonable that a higher risk of ischemic events with morphine restricted to patients treated with concomitant clopidogrel is most likely explained by a clinical interaction between these drugs, which is highly consistent with the pharmacological studies (4,8).

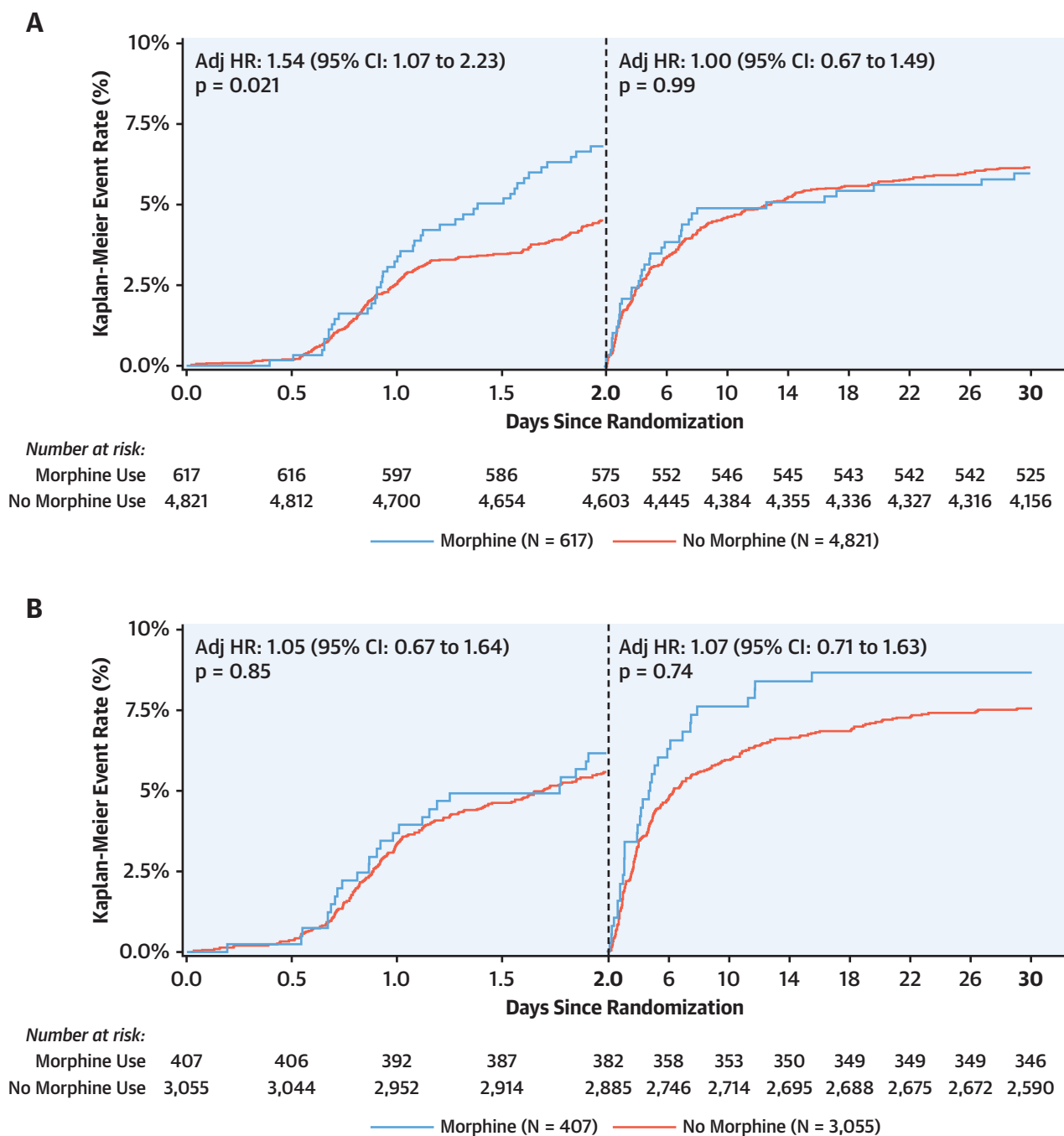
**COMPARISON WITH OTHER PRIOR STUDIES.** One of the first reports of a concern with morphine in ACS came from the CRUSADE registry, which showed that morphine use in the first 24 h of hospitalization was associated with higher in-hospital mortality and MI in patients presenting with NSTEMI/UA (14). In that report, inverse causality bias may have

been present, because morphine use was considered within the first 24 h of admission, and events of interest were in-hospital complications (before or after the first 24 h). In contrast, we took into account only morphine use before randomization so that the endpoints of interest were ascertained after that time point.

Subsequently, other registries tried to address the impact of morphine in clinical outcomes among patients with ACS, after the possible pharmacological drug interactions had been raised in the medical literature. In the FAST-MI registry, no association between pre-hospital morphine and death or MI in a cohort of patients with STEMI was observed (15). In FAST-MI, morphine-treated patients received better pre-hospital care, with greater use of reperfusion therapy, shorter door-to-balloon times, and more use of evidence-based medications than patients not treated with pre-hospital morphine. Even though adjusted models were performed, residual confounding related to the quality of care may have persisted in the analysis, thereby biasing results toward the null. Other studies have also reported no association between morphine use and decreased clinical efficacy with ADP receptor blockers in patients with STEMI, but the number of individuals in



**FIGURE 3** Kaplan-Meier Rates and Landmark Analysis



Death or MI at 30 days according to morphine use before randomization. **(A)** Patients treated with concomitant clopidogrel (N = 5,438). **(B)** Patients not receiving clopidogrel (N = 3,462). Adj HR = adjusted hazard ratio; CI = confidence interval; MI = myocardial infarction.

those reports was much smaller (17,18). Finally, in the ATLANTIC (Administration of Ticagrelor in the cath Lab or in the Ambulance for New ST elevation myocardial Infarction to open the Coronary artery)

trial, which randomly assigned patients with STEMI to an early (at ambulance) versus delayed (at coronary angiogram) ticagrelor loading dose, 1 of the coprimary endpoints, ST-segment resolution, was significantly

decreased by the early loading dose only in the subgroup of patients who did not receive pre-hospital morphine (16).

**IMPLICATIONS FOR FUTURE GUIDELINES.** Society guidelines continue to endorse morphine or other intravenous opioids for pain management in NSTEMI (2,3), although some have downgraded the recommendation after the first reports of possible harmful morphine effects (27). In 2018, the FDA updated all currently used oral ADP receptor blocker labels regarding this issue, and the European Medicines Agency made similar recommendations (11–13,28,29). However, those warnings were based mostly on mechanistic evidence because published data regarding clinical outcomes have been conflicting. That said, our results, although not definitive, provide important new information for both society NSTEMI guidelines and regulatory agencies. Ultimately, this issue would be best evaluated by a randomized clinical outcomes trial.

**IMPLICATIONS FOR FUTURE RESEARCH.** Given the paucity of effective non-narcotic options for pain management in NSTEMI, our results are intended to encourage new investigation on alternative treatments. Replacing morphine with other opioids may be a reasonable approach. However, the randomized placebo-controlled PACIFY (Platelet Aggregation With Ticagrelor Inhibition and Fentanyl) trial showed that fentanyl blunted ticagrelor effect and led to more myocardial damage (assessed by high-sensitivity troponin) during elective PCI, thus raising concerns that this interaction could be a class effect from all opioids (10). To further investigate this issue, the PERSEUS (Platelet Inhibition After Pre-hospital Ticagrelor Using Fentanyl Compared to Morphine in Patients With ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention) trial (NCT02531165) will randomly assign 56 patients with STEMI undergoing primary PCI and treated with ticagrelor to receive morphine versus fentanyl and will assess platelet reactivity as the primary endpoint (30). Recently, the intravenous peripheral opioid receptor antagonist methylnaltrexone was not shown to improve ticagrelor pharmacokinetics and pharmacodynamics in patients being administered with morphine and a loading dose of ticagrelor concomitantly (31). One reasonable option could be the use of intravenous glycoprotein IIb/IIIa inhibitors. In our study, morphine was associated with higher rates of ischemic outcomes at 96 h regardless of the randomized treatment strategy. However, the EARLY ACS trial was not testing eptifibatide versus no eptifibatide but, instead, 2 different

strategies (routine early vs. delayed, provisional use of the drug), and the early strategy was not superior to the delayed one in the main trial (22). Other strategies, such as crushed oral antiplatelet drugs, concomitant administration of prokinetic medications, or replacing oral ADP receptor blocker with an intravenous agent such as cangrelor, deserve further investigation (32–34).

**STUDY STRENGTHS AND LIMITATIONS.** Our study has some strengths that should be mentioned. First, we found consistent results in 2 different adjusted models (IPTW and logistic regression), which were used to adjust for imbalances between the 2 groups regarding baseline characteristics and concomitant treatments. Second, we found no such association in the cohort of patients not pre-treated with concomitant clopidogrel, which makes the hypothesis being tested, that is, that the pharmacokinetic interaction between morphine and clopidogrel may have clinical impact, more plausible. Moreover, both the absence of any association between morphine and ischemic events occurring after the first 48 h (landmark analysis) and the absence of any association between morphine use and noncardiovascular events (falsification endpoints) also support the hypothesis being tested. Finally, the fact that in our study all events were centrally adjudicated by a clinical events committee, different from other prior similar reports on the same topic (14,15,18,19), provides more consistency and reliability to our findings.

We acknowledge that our study has limitations. First, as with any observational report, we cannot establish a definitive causal relationship because the results may be related to unmeasured confounders. However, we used adjusted analyses, and, different from other reports, we also looked for falsification endpoints. If higher risk with morphine was due only to confounding by indication (i.e., sicker patients were more likely to receive morphine), we would expect to see an increase in other noncardiovascular adverse events unrelated to the proposed hypothesis of drug interaction. Also, we did not see higher rates of bleeding with morphine, which argues against the hypothesis that patients treated with morphine were higher risk despite our adjustments. Furthermore, the observation that landmark analysis did not show any excess ischemic risk after the first 48 h and that an excess risk was not found in individuals not pre-treated with clopidogrel reinforce the hypothesis being tested. Another limitation is that the exact time of morphine administration was not recorded. However, because the inclusion criteria from the EARLY ACS trial required eligible individuals to be enrolled

within the first 12 h of hospital presentation and within 24 h of symptoms onset, it is likely that clopidogrel and morphine before randomization were taken within a few hours of each other. The administration of morphine after clopidogrel would have biased toward the null, and our findings may indeed be an underestimate of the true association. Third, we did not record the use of other opioids, such as fentanyl, but this would also bias the results toward the null. Fourth, we cannot extrapolate our findings to other oral ADP receptor blockers. It might be possible that, due to their faster onset of action and higher levels of platelet inhibition, our findings may not apply to prasugrel and ticagrelor (35,36). However, data from mechanistic studies have shown the same interaction with prasugrel and ticagrelor (6–10). Therefore, those interactions seem to be a class effect for oral ADP blockers and are not only drug specific. Fifth, we exclusively studied patients with NSTEMI, for which the need for pre-treatment with oral ADP receptor blockers is currently disputed. Thus, the impact of morphine on ischemic events could be less relevant compared with STEMI; however, mechanistic studies have also shown the pharmacological interaction between opioids and oral ADP receptor blockers in patients with STEMI (6,8,9). Sixth, although there was a significant association between morphine use and cardiovascular outcomes in patients pre-treated with clopidogrel and no association in those who were not (our negative control), the interaction term did not reach nominal statistical significance. Finally, the low number of deaths precludes any conclusion regarding the relationship of the interactions described here with all-cause mortality.

## CONCLUSIONS

Among patients presenting with a high-risk, invasively managed NSTEMI, concomitant morphine use with clopidogrel pre-treatment was associated with higher adjusted risk of short-term cardiac ischemic events compared with clopidogrel without morphine. This finding suggests that prior data from mechanistic studies showing drug interaction between opioids and oral ADP receptor blockers may impact clinical outcomes.

**ADDRESS FOR CORRESPONDENCE:** Dr. Robert P. Giugliano, TIMI Study Group, Hale Building of Transformative Medicine, 60 Fenwood Road, Suite 7022, Boston, Massachusetts 02115. E-mail: [rgiugliano@bwh.harvard.edu](mailto:rgiugliano@bwh.harvard.edu). Twitter: @rgiugliano.

## PERSPECTIVES

### COMPETENCY IN PATIENT CARE AND PROCEDURAL

**SKILLS:** Morphine may attenuate the antiplatelet effect of clopidogrel and increase the risk of secondary ischemic events in patients with non-ST-segment elevation acute coronary syndromes undergoing coronary angiography.

**TRANSLATIONAL OUTLOOK:** Additional research is needed to define the pharmacological interactions between analgesic and antithrombotic medications in patients with acute coronary syndromes.

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**KEY WORDS** ADP receptor blocker, clopidogrel, drug interaction, non-ST-segment elevation ACS, opioids

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**APPENDIX** For an expanded Methods section as well as supplemental tables and figures, please see the online version of this paper.