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ORIGINAL RESEARCH ARTICLE

Morphine and Ticagrelor Interaction in Primary Percutaneous Coronary Intervention in ST-Segment Elevation Myocardial Infarction: ATLANTIC-Morphine

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Abstract

Background Morphine adversely impacts the action of oral adenosine diphosphate (ADP)-receptor blockers in ST-segment elevation myocardial infarction (STEMI) patients, and is possibly associated with differing patient characteristics. This retrospective analysis investigated whether interaction between morphine use and pre-percutaneous coronary intervention (pre-PCI) ST-segment elevation resolution in STEMI patients in the ATLANTIC study was associated with differences in patient characteristics and management.

Methods ATLANTIC was an international, multicenter, randomized study of treatment in the acute ambulance/hospital setting where STEMI patients received ticagrelor 180 mg ± morphine. Patient characteristics, cardiovascular history, risk factors, management, and outcomes were recorded.

Results Opioids (97.6% morphine) were used in 921 out of 1862 patients (49.5%). There were no significant differences in age, sex or cardiovascular history, but more morphine-treated patients had anterior myocardial infarction and left-main disease. Time from chest pain to electrocardiogram and ticagrelor loading was shorter with morphine (both $p = 0.01$) but not total ischemic time. Morphine-treated patients more frequently received glycoprotein IIb/IIIa inhibitors ($p = 0.002$), thromboaspiration and stent implantation (both $p < 0.001$). No significant difference between the two groups was found regarding pre-PCI ≥ 70% ST-segment elevation resolution, death, myocardial infarction, stroke, urgent revascularization and definitive acute stent thrombosis. More morphine-treated patients had an absence of pre-PCI Thrombolysis in Myocardial Infarction (TIMI) 3 flow (85.8% vs. 79.7%; $p = 0.001$) and more had TIMI major bleeding (1.1% vs. 0.1%; $p = 0.02$).

Conclusions Morphine-treatment was associated with increased GP IIb/IIIa inhibitor use, less pre-PCI TIMI 3 flow, and more bleeding. Judicious morphine use is advised with non-opioid analgesics preferred for non-severe acute pain.

Trial Registration clinicaltrials.gov identifier: NCT01347580.

1 Introduction

The interaction between morphine and oral antiplatelet therapy is a current subject of interest, recently brought to the fore by the results of the Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery (ATLANTIC) study (NCT01347580). ATLANTIC evaluated in-ambulance versus in-hospital (in-catheterization laboratory [cath lab]) administration of ticagrelor loading dose in patients with ST-segment elevation myocardial infarction (STEMI) with planned primary percutaneous

The full list of ATLANTIC investigators is shown in the Acknowledgements section.

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coronary intervention (PCI). The results showed no benefit in terms of coronary reperfusion, as evaluated by the co-primary endpoints (absence of ≥ 70% ST-segment elevation resolution and/or Thrombolysis in Myocardial Infarction [TIMI] 3 flow in the culprit artery, measured just before PCI) [1]. Approximately half (49.5%) of all patients in the ATLANTIC study were treated with opioids, predominantly morphine. Sub-group analysis showed a significant interaction between morphine use and timing of ticagrelor administration, and the ST-segment elevation resolution co-primary endpoint (p value for interaction = 0.005). In this respect, pre-hospital administration of ticagrelor was superior to in-hospital administration in patients who did not receive morphine. This strongly suggested a negative impact of morphine administration on the onset of action of oral adenosine diphosphate receptor blockers in STEMI patients.

It should be remembered that morphine has long been indicated in the treatment of patients with acute myocardial infarction (MI), despite an absence of high-level evidence supporting this recommendation. Accordingly, most STEMI networks use morphine in the majority of patients for pain relief and reduction of emotional impact. However, retrospective analysis of real-life data from the Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines (CRUSADE) initiative highlighted a negative impact of morphine prescription on mortality [2]. In 2007, this finding contributed to the downgrading (from level I to IIa) of the recommendation for morphine use in the management of patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS) [3]. The CRUSADE observations, like those of the ATLANTIC study, raise the question of the potential mechanisms of interaction between morphine and oral antiplatelet therapy. This interaction between morphine and ticagrelor has been prospectively demonstrated in a recent randomized study [15]. Several assumptions have been made to explain the results, including vomiting, which would prevent the absorption of drugs; slowed gut transit, which would limit or delay drug absorption; or hemodynamic effects of morphine that would be unfavorable to coronary perfusion. There are also preclinical data suggesting that morphine may increase platelet reactivity by binding to α_2-adrenoceptors in platelets [4, 5].

Another hypothesis is that the characteristics of patients who receive morphine differ from those who do not, resulting in different management and outcomes. The ATLANTIC study presents an opportunity to evaluate this hypothesis in STEMI patients, to determine whether the observed interaction between morphine use and pre-PCI ST-segment elevation resolution could be explained by differences in patient characteristics and management, or by a direct effect of morphine itself. We present here the results of this analysis.

2 Methods

2.1 Study Design

The international, multicenter ATLANTIC trial was conducted by the ACTION group at the Institut de Cardiologie, Hôpital Pitié-Salpêtrière, Paris, France (www.action-coeur.org) and funded by AstraZeneca. Detailed methods and results have been published previously [1, 6]. In summary, patients diagnosed with STEMI (< 6 h from onset) and scheduled for primary PCI were randomized in the pre-hospital setting to receive a pre- versus in-hospital ticagrelor 180-mg loading dose. The co-primary endpoint was absence of pre-PCI ≥ 70% ST-segment elevation resolution and/or TIMI flow grade 3 in the infarct-related artery at initial angiography. Other treatments, including anticoagulants, glycoprotein (GP) IIb/IIIa inhibitors and morphine, were left to the physician's discretion.

The aim of this analysis was to compare patients who received morphine and those who did not in terms of (1) prior cardiovascular history (STEMI, PCI, coronary artery bypass graft [CABG], transient ischemic attack, hemorrhagic stroke, and ischemic stroke) and risk factors (hypertension, dyslipidemia, diabetes, chronic obstructive pulmonary disease [COPD], and renal disease); (2) initial clinical features, including indicators of risk/severity (e.g., TIMI risk score and Killip class > 1); (3) culprit artery; (4) management, including use of anticoagulants, bail-out GP IIb/IIIa inhibitor use, sheath insertion site, thromboaspiration and timing (from chest pain to electrocardiogram [ECG] and loading dose, from chest pain and ECG to PCI, and between pre- and in-hospital ticagrelor loading dose); and (5) other ATLANTIC endpoints, including the co-primary endpoints (absence of pre-PCI ≥ 70% ST-segment elevation resolution and TIMI 3 flow in the culprit artery), clinical efficacy (death, MI, stroke, urgent revascularization, and stent thrombosis) and safety (bleeding events and severity according to PLATO, GUSTO, TIMI and STEEPLE definitions).

2.2 Data Management

Data management for the substudy variables was performed by AstraZeneca using an extraction of the case report forms (CRF) of the ATLANTIC trial. Of note, morphine administration was captured in the initial CRF and used for evaluation of any interaction with platelet inhibition.

2.3 Statistical Methods

Subjects were classified according to morphine use for the index event or PCI. Comparisons between the two groups

for baseline and peri-procedural characteristics were performed using Chi squared tests for categorical variables and Student's *t* tests for continuous variables. The association between morphine use and the co-primary endpoints was assessed by fitting logistic regression models with morphine use as the only covariate, for those subjects with data available for the relevant endpoint. The relationship between morphine use and the clinical efficacy and bleeding outcomes within 24 h of the first loading dose of study medication was investigated similarly. Co-primary endpoints were analyzed as combinations of death, MI, stroke AND/OR urgent revascularization AND/OR definitive stent thrombosis AND/OR bail-out use of GP IIb/IIIa inhibitors. Bleeding outcomes were evaluated in patients who underwent PCI for the index event.

Continuous variables are presented as mean and standard deviation (SD) or median and minimum–maximum values, as appropriate. Categorical variables are presented as counts and percentages.

All analyses were performed using SAS, version 9.3 (©2010, SAS Institute Inc., USA).

3 Results

3.1 Patient Characteristics and Management

The ATLANTIC study included 1862 patients randomized in 13 countries (Algeria, Australia, Canada, and ten European countries) [1]. Morphine/opioids were used in 921 patients (49.5%) (450/909 [49.5%] randomized to pre-hospital ticagrelor and 471/953 [49.4%] in-hospital ticagrelor) (Fig. 1). Internationally, the median (interquartile range) proportion of patients receiving morphine was 47% (45–60%), ranging from 0% (Algeria) to 86% (Australia).

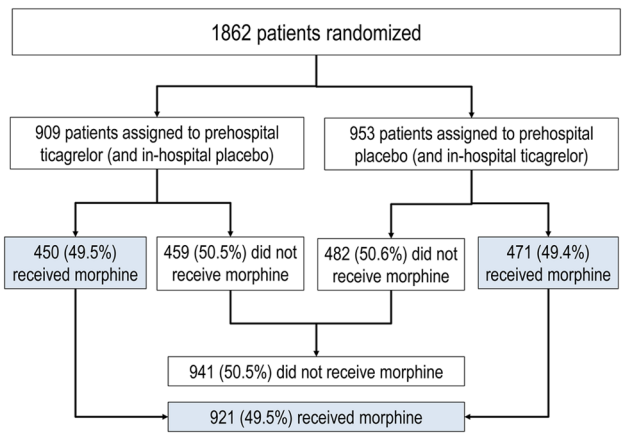

Fig. 1 CONSORT flow diagram

Some patients received more than one opioid, which consisted of morphine in 899 (97.6%) of the 921 patients, codeine with caffeine in 47 (5.1%), and oxycodone in six (0.7%). The percentages of each type of opioid administered were very similar in the ticagrelor pre- and in-hospital treatment groups. Opioid administration was intravenous in 881 cases (95.7%), oral in 61 (6.6%), subcutaneous in 19 (2.1%), and other or unknown in three (0.3%).

There was no significant difference between patients receiving morphine and other patients in terms of age, sex or prior cardiovascular history and risk factors (Table 1). Overall, the main indicators of risk or severity were generally similar in patients who did or did not receive morphine, but significantly more of those treated with morphine had a body mass index ≥ 30 kg/m^2 (22.3% vs. 15.9%, $p < 0.001$), whereas fewer underwent secondary transfer (21.0% vs. 27.2%, $p < 0.01$). Diagnostic delays (chest pain to ECG) and management delays (chest pain to loading dose of ticagrelor or placebo) were significantly shorter in patients who received morphine [median (range) 68 (3–1802) vs. 78 (7–2904) min, $p < 0.01$; and 85 (15–1810) vs. 97 (16–2920) min, $p = 0.01$, respectively] (Table 1). The total ischemic time (chest pain to PCI) was not significantly different between the groups [155 (57–6345) vs. 163 (50–4231) min, $p = 0.2$]. There were significant differences in terms of culprit coronary artery ($p < 0.0001$), notably for left anterior descending (more likely in morphine-treated patients, 43.0% vs. 34.9%) and no culprit vessel identified (less likely in morphine-treated patients, 3.8% vs. 8.5%). Patients receiving morphine were significantly more likely to be treated with GP IIb/IIIa inhibitors (41.9% vs. 34.8%, $p < 0.01$), and were more likely to undergo thromboaspiration (54.7% vs. 46.4%, $p < 0.001$) and PCI (91.6% vs. 83.5%, $p < 0.0001$) (Table 1).

3.2 Outcomes

Significantly more morphine-treated patients had an absence of pre-PCI TIMI 3 flow (85.8% vs. 79.7%; $p = 0.001$), and/or absence of pre-PCI ≥ 70% ST-segment elevation resolution (77.1% vs. 68.9%; $p < 0.001$) (Table 2 and Fig. 2). There was also a trend towards more morphine patients with an absence of pre-PCI ≥ 70% ST-segment elevation resolution (88.8% vs. 85.7%; $p = 0.07$) and an absence of the combined endpoint (95.5% vs. 93.1%; $p = 0.05$).

Significant differences were observed in the morphine versus no morphine groups for bail-out use of GP IIb/IIIa inhibitors within 24 h of the first loading dose (11.3% vs. 7.9%, respectively; $p = 0.01$) (Table 2). The composite endpoint of death/MI/urgent revascularization/definite acute stent thrombosis/bail-out use of GP IIb/IIIa inhibitors was also significantly different for morphine versus no morphine (12.7% vs. 9.4%; $p = 0.02$), but this was driven by the GP IIb/IIIa inhibitors component. No differences

Table 1 Patient characteristics and management according to morphine use (all randomized patients)

	Morphine ($n=921$)	No morphine ($n=941$)	P value
Patient demographics, cardiovascular history, and risk factors			
Age, years; mean (SD)	60.3 (12.2)	61.3 (12.7)	0.08
Age ≥ 65 years	320 (34.7)	363 (38.6)	0.09
BMI > 30 kg/m^2	205 (22.3)	150 (15.9)	< 0.001
Male	742 (80.6)	751 (79.8)	0.68
Prior cardiovascular history			
STEMI	81 (8.8)	78 (8.3)	0.70
PCI	67 (7.3)	73 (7.8)	0.69
CABG	5 (0.5)	7 (0.7)	0.59
Transient ischemic attack	9 (1.0)	13 (1.4)	0.42
Hemorrhagic stroke	1 (0.1)	4 (0.4)	0.19
Ischemic stroke	10 (1.1)	8 (0.9)	0.60
Risk factors			
Hypertension	407 (44.2)	388 (41.2)	0.20
Dyslipidemia	336 (36.5)	317 (33.7)	0.21
Diabetes mellitus	122 (13.2)	131 (13.9)	0.67
COPD	42 (4.6)	34 (3.6)	0.30
Chronic renal disease	16 (1.7)	18 (1.9)	0.78
Indicators of risk/severity, delays, culprit artery, and management			
TIMI risk score, mean (SD)	2.1 (1.9)	2.2 (1.9)	0.13
Killip class > I	87 (9.4)	94 (10.0)	0.69
Secondary transfer	193 (21.0)	256 (27.2)	< 0.01
Timing, minutes; median (min–max)			
Chest pain to ECG	68 (3–1802)	78 (7–2904)	< 0.01
Chest pain to LD	85 (15–1810)	97 (16–2920)	0.01
ECG to PCI	80 (31–6295)	81 (26–4167)	0.76
Pre- vs. in-hospital LD	30 (0–725)	32 (0–1263)	0.18
Chest pain to PCI	155 (57–6345)	163 (50–4231)	0.20
ECG to PCI	80 (31–6295)	81 (26–4167)	0.76
Culprit coronary artery[a]			< 0.0001
Left anterior descending	393 (43.0)	319 (34.9)	
Right coronary	353 (38.7)	387 (42.3)	
Left circumflex	115 (12.6)	120 (13.1)	
Left main	14 (1.5)	8 (0.9)	
Saphenous vein graft	3 (0.3)	2 (0.2)	
No culprit vessel	35 (3.8)	78 (8.5)	
Management			
Intravenous anticoagulation	822 (89.3)	820 (87.1)	0.16
Radial sheath insertion[a]	628 (68.8)	601 (65.8)	0.16
GP IIb/IIIa inhibitors	386 (41.9)	327 (34.8)	< 0.01
Procedures for index event			
Thromboaspiration	504 (54.7)	437 (46.4)	< 0.001
PCI	844 (91.6)	786 (83.5)	< 0.0001
Any stent(s)	792 (86.0)	744 (79.1)	< 0.0001
DES	495 (53.7)	451 (47.9)	0.01
BMS	314 (34.1)	303 (32.2)	0.39
CABG	13 (1.4)	12 (1.3)	0.80
No PCI or CABG	64 (6.9)	143 (15.2)	< 0.0001

Values are *n* (%) unless otherwise indicated

BMI body mass index, *BMS* bare-metal stent, *CABG* coronary artery bypass graft, *COPD* chronic obstructive pulmonary disease, *DES* drug-eluting stent, *ECG* electrocardiogram, *GP* glycoprotein, *LD* loading dose, *PCI* percutaneous coronary intervention, *SD* standard deviation, *STEMI* ST-segment elevation myocardial infarction, *TIMI* Thrombolysis in Myocardial Infarction

[a]Data available for 1827 patients ($n=913$ morphine, $n=914$ no morphine)

Table 2 Co-primary endpoints and clinical endpoints within 24 h of first loading dose according to morphine use (modified intention-to-treat population)

	Morphine ($n=921$)		No morphine ($n=937$)		Odds ratio for morphine vs. no morphine (95% CI) (value > 1 favors no morphine)	*P* value
	n evaluable	*n* (%) with endpoint	*N* evaluable	*N* (%) with endpoint		
Co-primary endpoint						
Absence of pre-PCI TIMI 3 flow in culprit artery	867	744 (85.8)	813	648 (79.7)	1.54 (1.19, 1.99)	0.001
Absence of pre-PCI ≥ 70% ST-segment elevation resolution	800	710 (88.8)	798	684 (85.7)	1.32 (0.98, 1.77)	0.07
Absence of pre-PCI TIMI 3 flow in culprit artery AND/OR pre-PCI ≥ 70% ST-segment elevation resolution	781	602 (77.1)	740	510 (68.9)	1.52 (1.21, 1.91)	< 0.001
Absence of pre-PCI TIMI 3 flow in culprit artery AND pre-PCI ≥ 70% ST-segment elevation resolution	757	723 (95.5)	713	664 (93.1)	1.57 (1.00, 2.46)	0.05
Clinical endpoints within 24 h of first loading dose						
Death/MI/stroke/urgent revascularization	921	16 (1.7)	937	10 (1.1)	1.64 (1.74, 3.63)	0.22
Death/MI/urgent revascularization/definite acute stent thrombosis	921	17 (1.8)	937	15 (1.6)	1.16 (0.57, 2.33)	0.685
Death/MI/stroke/urgent revascularization/definite acute stent thrombosis	921	18 (2.0)	937	16 (1.7)	1.15 (0.58, 2.26)	0.69
Death/MI/urgent revascularization/definite acute stent thrombosis/bail-out use of GP IIb/IIIa inhibitors	921	117 (12.7)	937	88 (9.4)	1.40 (1.05, 1.88)	0.02
MI/definite acute stent thrombosis	921	5 (0.5)	937	8 (0.9)	0.63 (0.21, 1.95)	0.43
All-cause mortality	921	10 (1.1)	937	6 (0.6)	1.70 (0.62, 4.71)	0.30
MI	921	4 (0.4)	937	2 (0.2)	2.04 (0.37, 11.18)	0.41

Table 2 (continued)

	Morphine ($n=921$)		No morphine ($n=937$)		Odds ratio for morphine vs. no morphine (95% CI) (value > 1 favors no morphine)	*P* value
	n evaluable	*n* (%) with endpoint	*N* evaluable	*N* (%) with endpoint		
Urgent revascularization	921	4 (0.4)	937	2 (0.2)	2.04 (0.37, 11.18)	0.41
Definite acute stent thrombosis	921	2 (0.2)	937	6 (0.6)	0.34 (0.07, 1.68)	0.18
Bail-out use of GP IIb/IIIa inhibitors	921	104 (11.3)	937	74 (7.9)	1.48 (1.09, 2.03)	0.01
Stroke, any	921	1 (0.1)	937	1 (0.1)	1.02 (0.06, 16.29)	0.99

Values are *n* (%)

GP glycoprotein, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *TIMI* Thrombolysis in Myocardial Infarction

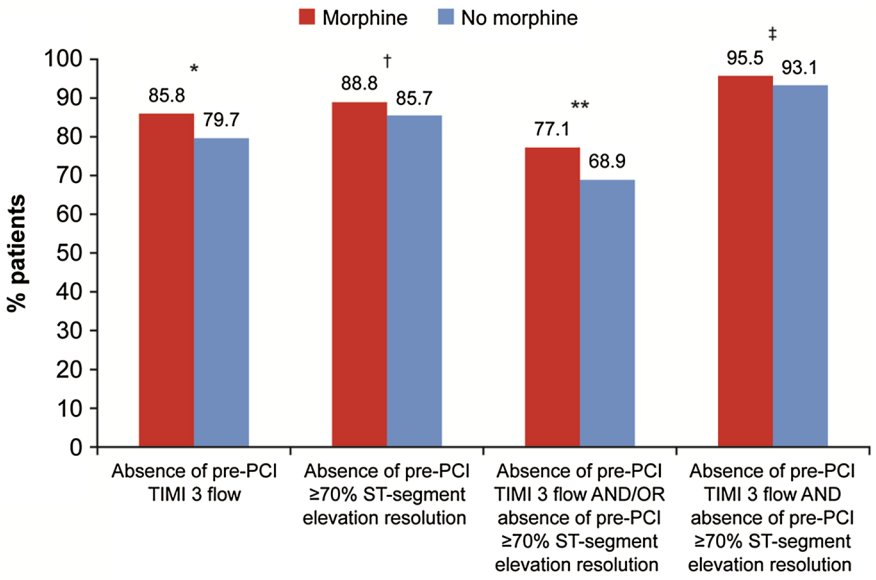

Fig. 2 Co-primary endpoints: absence of pre-percutaneous coronary intervention (pre-PCI) Thrombolysis in Myocardial Infarction (TIMI) 3 flow in culprit artery and/or ≥ 70% ST-segment elevation resolution (modified intention-to-treat population)

were found (all p = not significant) in individual endpoints for morphine versus no morphine for death, 1.1% versus 0.6%; MI, 0.4% versus 0.2%; urgent revascularization, 0.4% versus 0.2%; and definite stent thrombosis, 0.2% versus 0.6%. There was also a significantly higher rate of bleeding complications in the morphine-treated patients, particularly major bleeding, in most definitions (Supplementary Table 1, see the electronic supplementary material). For example, major bleeding within the first 24 h using the TIMI definition occurred in 1.1% with morphine versus 0.1% without ($p=0.02$), and major life-threatening/fatal bleeding using the PLATO definition occurred in 1.3% versus 0.3%, respectively ($p=0.02$).

4 Discussion

The results of this post hoc analysis of data from the ATLANTIC study show that patients who received morphine were generally similar to those who did not in terms of baseline characteristics and cardiovascular risk. However, those who received morphine more frequently had anterior MI and left-main disease, whereas those who did not less frequently had PCI or CABG, suggesting no significant coronary artery disease. They were also managed earlier and received more powerful antiplatelet treatment in the form of significantly greater use of GP IIb/IIIa inhibitors. Pre-PCI reperfusion, based on

the ATLANTIC study co-primary endpoint criteria, i.e., absence of pre-PCI ≥ 70% ST-segment elevation resolution and TIMI 3 flow at coronary angiography, was less favorable in morphine-treated patients. These results support the hypothesis of a direct interaction between morphine and antiplatelet drugs taken orally. Moreover, major bleeding complications were more frequent in morphine-treated patients, possibly related to the more frequent use of GP IIb/IIIa inhibitors.

Morphine-based analgesia is indicated for the management of patients with chest pain in the setting of acute coronary syndrome (ACS) with ST-segment elevation [7]. The treatment of pain is fundamental, both for patient comfort and because pain has adverse hemodynamic effects, such as increased heart rate, elevated blood pressure, and impaired coronary perfusion. There is also some evidence that morphine has cardioprotective effects, albeit derived mainly from animal models and relatively small clinical studies [8, 9]. However, the recommendation for morphine use is not based on any study with high-level evidence. On the other hand, evidence that other analgesics are efficient and safe in STEMI patients is very limited.

The main hypothesis proposed to explain the effects of morphine was an unfavorable hemodynamic effect. In an old study in which hemodynamic effects were particularly well documented, administration of morphine in critically ill patients was associated with a decrease in systolic blood pressure of 20 mmHg, a decrease in heart rate of 10 beats per minute and a reduced cardiac index of about 20% (with no effect on systemic vascular resistance) [10]. In a much more recent study, morphine use was associated with a significant increase in infarct size in patients with STEMI managed with primary PCI [11]. Similar experimental observations of the effects of nitrates on coronary blood flow and infarct size gradually led to their abandonment [12].

More recently, the possibility of an interaction between morphine and orally administered platelet aggregation inhibitors has been raised. A recent pharmacodynamic study in healthy volunteers showed that the use of morphine with clopidogrel reduced plasma concentrations of the active metabolite and decreased the antiplatelet effects of clopidogrel [13]. The authors concluded that morphine caused a "poor metabolizer" phenotype in individuals prone to extensively metabolize clopidogrel.

The increasing use of the latest generation of oral platelet aggregation inhibitors in the management of ACS has made this issue even more pertinent, and an interaction with morphine has been observed in several clinical studies, including ATLANTIC [1, 14–16]. In contrast, two small randomized studies in healthy volunteers found that, while plasma levels of ticagrelor or the active metabolite of prasugrel were reduced with morphine co-administration, there was no significant reduction in platelet inhibition [17, 18]. A further study indicated that morphine delayed the absorption of prasugrel and consequent platelet inhibition in patients with prior history of STEMI [19]. In the Influence of Morphine on Pharmacokinetics and Pharmacodynamics of Ticagrelor in Patients with Acute Myocardial Infarction (IMPRESSION) study, morphine altered both pharmacokinetic and pharmacodynamic ticagrelor properties. It delayed and attenuated ticagrelor action in STEMI patients [15]. In a recent report from the French Registry of Acute ST-elevation and non-ST-elevation Myocardial Infarction (FAST-MI) survey, STEMI patients who received morphine and those who did not had similar outcomes in terms of in-hospital complications and mortality at 1 year [20].

It was, therefore, considered crucial to scrutinize the results of the ATLANTIC study to better understand the potential mechanisms of the interaction with morphine. One hypothesis was that patients receiving morphine differed from other patients, but comparison of patient profiles, history and risk factors largely suggested otherwise. The usual severity markers, age, TIMI risk score and Killip class, were similar in both groups. Furthermore, time to diagnosis (ECG), a major prognostic criterion, was significantly shorter in patients who received morphine. Conversely, there was a higher proportion of morphine-treated patients with anterior MI or left-main disease, and greater use of thromboaspiration, which suggests larger thrombus burden.

The absence of adverse prognostic factors in the morphine group is a strong argument in favor of a direct effect of morphine. The well-known emetic effects of morphine implicated vomiting as a potential inhibitor of absorption of orally administered drugs. However, two recent studies observed only a small proportion of ACS patients who experienced vomiting (6%), making this an unlikely assumption [21]. Another study in STEMI patients found that morphine use was associated with high residual platelet reactivity even after the exclusion of patients who vomited [14]. It is likely, rather, that the absorption of orally administered drugs is delayed as a result of slowed gastrointestinal transit, a long-recognized effect of opioid administration [19, 22].

This ATLANTIC analysis also showed that morphine use was associated with a significantly greater incidence of ischemic and bleeding complications. Morphine contributed to reduced antiplatelet activity of oral agents [14]. This effect was confirmed in the PRIVATE-ATLANTIC study, a pre-specified pharmacodynamic substudy from the ATLANTIC trial [23]. Compared with other patients, those who received morphine had reduced inhibition of platelet aggregation, which became apparent at the time of angioplasty and was significantly different at 1 and 6 h post-PCI. It is unsurprising, therefore, that rates of ST-segment elevation resolution and coronary artery perfusion were reduced. There was also a general pattern in terms of fewer ischemic events in patients who did not

receive morphine, which is consistent with the electrocardiographic and angiographic results. Inadequate inhibition of platelet aggregation also explains the more frequent use of thromboaspiration (54.7% vs. 46.4%, $p < 0.001$) and GP IIb/IIIa inhibitors (41.9% vs. 34.8%, $p < 0.01$) in the morphine-treated group, including bail-out use of the latter (11.3% vs. 7.9%, $p = 0.01$). The drug–drug interaction between ticagrelor and morphine has been suggested in other studies [24–26] and may relate to poor outcomes in some trials [27]. We believe that the greater use of GP IIb/IIIa inhibitors explains the increase in bleeding complications in patients who received morphine. Thus, if the prescription of morphine was responsible for reduced inhibition of platelet aggregation and therefore a less favorable clinical course, it was also indirectly responsible for an increase in complications of adjuvant antiplatelet therapy. The delayed onset of platelet inhibition, as shown in PRIVATE-ATLANTIC, certainly contributed to this effect.

Non-opioid analgesics should be preferred for the treatment of non-severe acute pain. Although morphine is currently the key analgesic for severe acute pain, other agents, without adverse hemodynamic or gastrointestinal effects, should be tried. Finally, it is worth noting that the absorption of oral antiplatelet agents can be improved by crushing the tablets prior to administration, as recently shown in the Mashed Or Just Integral Pill of TicagrelOr (MOJITO) study [16].

In terms of limitations, the intensity of the pain that led to the prescription of morphine was not prospectively collected in the ATLANTIC study. Therefore, the possibility of an interaction between pain intensity, MI severity and its evolution cannot be formally excluded. However, this remains highly theoretical since there is no solid scientific argument for an interaction between pain intensity and diagnosis or severity of ACS [28]. Similarly, the precise modalities of morphine administration were not prospectively collected in the ATLANTIC study. However, the simple observation of the interaction between morphine and inhibition of platelet aggregation renders unlikely the hypothesis of a confounding factor related to methods of administration of morphine. Conversely, the absence of TIMI 3 flow, indicating persistent ischemia could justify an increased morphine administration. However, it does not challenge the interaction between opiates and anti-platelet therapy. Finally, the international variability in frequency of morphine use suggests that there may be local algorithms/pathways that contribute to routine versus no use of morphine.

In conclusion, STEMI patients who received morphine within the ATLANTIC study had a less favorable ischemic outcome (i.e., pre-PCI TIMI 3 flow), possibly explained by a lower inhibition of platelet aggregation. They also had an increased use of GP IIb/IIIa inhibitors and more bleeding complications.

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