Effect of treatment delay on the effectiveness and safety of antifibrinolytics in acute severe haemorrhage: a meta-analysis of individual patient-level data from 40 138 bleeding patients

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Summary

Background Antifibrinolytics reduce death from bleeding in trauma and post-partum haemorrhage. We examined the effect of treatment delay on the effectiveness of antifibrinolytics.

Methods We did an individual patient-level data meta-analysis of randomised trials done with more than 1000 patients that assessed antifibrinolytics in acute severe bleeding. We identified trials done between Jan 1, 1946, and April 7, 2017, from MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, PubMed, Popline, and the WHO International Clinical Trials Registry Platform. The primary measure of treatment benefit was absence of death from bleeding. We examined the effect of treatment delay on treatment effectiveness using logistic regression models. We investigated the effect of measurement error (misclassification) in sensitivity analyses. This study is registered with PROSPERO, number 42016052155.

Findings We obtained data for 40 138 patients from two randomised trials of tranexamic acid in acute severe bleeding (traumatic and post-partum haemorrhage). Overall, there were 3558 deaths, of which 1408 (40%) were from bleeding. Most (884 [63%] of 1408) bleeding deaths occurred within 12 h of onset. Deaths from post-partum haemorrhage peaked 2–3 h after childbirth. Tranexamic acid significantly increased overall survival from bleeding (odds ratio [OR] 1·20, 95% CI 1·08–1·33; p=0·001), with no heterogeneity by site of bleeding (interaction p=0·7243). Treatment delay reduced the treatment benefit (p<0·0001). Immediate treatment improved survival by more than 70% (OR 1·72, 95% CI 1·42–2·10; p<0·0001). Thereafter, the survival benefit decreased by 10% for every 15 min of treatment delay until 3 h, after which there was no benefit. There was no increase in vascular occlusive events with tranexamic acid, with no heterogeneity by site of bleeding (p=0·5956). Treatment delay did not modify the effect of tranexamic acid on vascular occlusive events.

Interpretation Death from bleeding occurs soon after onset and even a short delay in treatment reduces the benefit of tranexamic acid administration. Patients must be treated immediately. Further research is needed to deepen our understanding of the mechanism of action of tranexamic acid.

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Introduction

Acute severe bleeding is a leading cause of death.[1] Traumatic extracranial haemorrhage, often the consequence of road traffic crashes or violence, is responsible for more than two million deaths each year.[2] Traumatic and spontaneous intracranial bleeding are common causes of death and disability.[3] Severe surgical haemorrhage strongly predicts adverse patient outcomes and is associated with an increase in the odds of death by eight times.[4] Thousands of patients are admitted to hospital with gastrointestinal bleeding each year in the UK, with a case fatality of about 10% for upper gastrointestinal bleeding and 3% for lower gastrointestinal bleeding.[5,6] Post-partum haemorrhage accounts for about 100 000 maternal deaths each year worldwide, with the majority occurring in less-developed countries.[7]

Antifibrinolytic drugs (tranexamic acid, aminocaproic acid, aprotinin, and aminomethylbenzoic acid) reduce bleeding by inhibiting the breakdown of fibrin clots.[8,9] Antifibrinolytics reduce surgical bleeding and the need for transfusion by about a third, irrespective of the site of surgery.[10] Administration of tranexamic acid within 3 h of bleeding onset reduces deaths from bleeding in patients with trauma and post-partum haemorrhage.[11–13] We sought to quantify the effect of treatment delay on the effectiveness of antifibrinolytics in acute severe bleeding by analysing individual patient-level data from randomised placebo-controlled trials.

Research in context

Evidence before this study

We sought to identify whether the benefits and harms of antifibrinolytic treatment vary by site of bleeding and time to treatment, by doing an individual patient-level data meta-analysis of relevant randomised trials done with more than 1000 participants. Systematic searches of MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, WHO International Clinical Trials Registry Platform, and ClinicalTrials.gov identified two randomised trials that assessed the effect of time to treatment in subgroup analyses (treatment started less than or more than 3 h since bleeding onset). Both trials had a low risk of bias and both showed that starting tranexamic acid within 3 h of bleeding onset reduced death from bleeding. However, no studies examined whether the effects of treatment varied by site of bleeding or explored the continuous association between treatment delay and the effectiveness and safety of antifibrinolytics.

Added value of this study

This individual patient-level data meta-analysis comprises data on 40 138 bleeding patients from two large trials in traumatic and post-partum bleeding. Most deaths from haemorrhage occur within hours of bleeding onset. We found no evidence that the effectiveness and safety of tranexamic acid varied by site of bleeding but found strong evidence that treatment delay reduces the survival benefit of tranexamic acid administration. Whereas immediate treatment greatly increases the odds of survival, the benefit decreases by about 10% for every 15 min of treatment delay until 3 h, after which there is no benefit.

Implications of all the available evidence

Patients with acute severe bleeding should receive antifibrinolytic treatment as soon as possible after bleeding onset. Trauma patients should be treated at the scene of injury and post-partum haemorrhage should be treated as soon as the diagnosis is made. Clinical audit should record the time from bleeding onset to tranexamic acid treatment, with feedback and best practice benchmarking.

Methods

Search strategy and selection criteria

We did an individual patient-level data meta-analysis of randomised placebo-controlled trials done with more than 1000 patients that assessed the effects of antifibrinolytics (including aprotinin, tranexamic acid, aminocaproic acid, and aminomethylbenzoic acid) in acute severe bleeding. We identified trials done between Jan 1, 1946, and April 7, 2017, from a register of antifibrinolytic trials maintained by the London School of Hygiene & Tropical Medicine Clinical Trials Unit. The register comprises MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, PubMed, Popline, and the WHO International Clinical Trials Registry Platform (appendix). Abstracts were screened for relevant trials and selection criteria were applied. Reasons for exclusion were discussed and discrepancies were solved by consensus. Two reviewers (AG-A and KK) independently extracted data to minimise bias. We analysed individual patient-level data for baseline, outcome, and predictor variables (treatment delay reported in the CRASH-2 trial, dates of randomisation and dates of death in CRASH-2, dates and times of randomisation, and births and deaths in the WOMAN trial) from the selected trials. We prepared a statistical analysis plan before searching for trials. We registered the study protocol in November, 2016 (PROSPERO, number 42016052155). Institutional review board approval was not required.

See Online for appendix

For the **study protocol** see http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42016052155

Outcomes

The primary measure of treatment benefit was absence of death from bleeding (ie, survival from bleeding or death from other causes). Death due to bleeding was chosen as the primary outcome because of the mechanism of action of antifibrinolytic drugs. These drugs inhibit the breakdown of fibrin clots and reduce bleeding. All-cause mortality is a composite outcome that combines deaths likely to be affected by antifibrinolytic treatment (eg, deaths from bleeding) with those unlikely to be affected by treatment (eg, sepsis), and this outcome would bias the relative risk towards the null.[14,15] Although some authors believe that tranexamic acid decreases trauma mortality by preventing inflammation, there is little evidence to support this hypothesis and the main effect of tranexamic acid is a reduced risk of exsanguination on the day of injury.[16] Secondary outcomes were vascular occlusive fatal and non-fatal events (myocardial infarction, stroke, pulmonary embolism, and deep vein thrombosis).

We evaluated the quality of the clinical trials selected by assessing sequence generation, allocation concealment, blinding, data completeness, and risk of selective reporting. Two reviewers (AG-A and KK) independently rated the risk of bias according to established criteria.[17]

We estimated treatment delay as the interval between bleeding onset and start of antifibrinolytic treatment. In the CRASH-2 trial, clinicians reported treatment delay. In the WOMAN trial, we estimated treatment delay as the interval between birth and randomisation.

Data analysis

All analyses were done according to the intention-to-treat principle. Data analysis was based on individual patient-level data. For continuous variables, we have reported the mean, SD, and median (IQR). For

categorical variables, we have reported numbers and proportions. We plotted frequency distributions for treatment delay and time to death from bleeding for each trial. We assessed the natural history of death from bleeding by plotting frequency distributions of hours to death from bleeding among untreated women with post-partum haemorrhage. We compared patients who died from exsanguination and were treated within the first hour with those who received later treatment, by use of the χ^2 test (type of injury, sex) or Student's t test (age, systolic blood pressure, heart rate, and volume of blood loss). We have reported deaths and vascular occlusive events by treatment allocation for each trial and overall.

We examined the effectiveness of antifibrinolytics on binary outcomes using logistic regression. We have reported treatment effects with odds ratios (OR) and 95% CI. We expressed the effect of antifibrinolytics on survival as the OR for absence of death from bleeding (relative treatment benefit). We first assessed the homogeneity of the treatment effects between trials by including an interaction term between the treatment and the trial variable and reporting the p value (model 1, appendix).[18] We anticipated that treatment effect might be affected negatively by treatment delay and explored the effect of treatment delay on treatment effect by including terms for hours of treatment delay and its square (because of the non-linearity of the treatment effect), and interactions between these two variables with treatment group. To check the homogeneity of the effect of treatment delay across trials, we ran a second model with a triple interaction between the terms for treatment delay, the treatment group, and the trial (model 2, appendix). Once homogeneity of the effect of treatment delay across trials was verified, we reported results from a third model including the two interaction terms (model 3, appendix). We quantified the effect of treatment delay on treatment effectiveness by estimating $[100-(\text{OR at time } t-1) / (\text{OR at } t=0-1)\times 100]$, corresponding to the percentage reduction in maximal effectiveness at interval t by use of ORs from model 3. The biological plausibility of model 3 was assessed by reporting relative treatment benefits stratified by 60-min intervals of treatment delay. Because the effect of delay on treatment effectiveness might be confounded by bleeding severity, all models were controlled for systolic blood pressure (5 mm Hg intervals) and age (10-year intervals), which are strong risk factors for death due to bleeding.[19]

Because the time of bleeding onset (ie, time of injury) is often unknown in trauma patients, measurement error is inevitable. We investigated the effect of misclassification of treatment delay in sensitivity analyses using a range of plausible errors.[20] We added a random number of minutes to the treatment delay using a uniform distribution with a constant minimum set at 0 and four sets of maximum value: 15, 30, 45, and 60 min in the CRASH-2 dataset only. The corrections were based on data from an audit of treatment delay in a similar trial in traumatic brain injury (the CRASH-3 trial), in which treatment delay was rarely overestimated but often underestimated (mean underestimation 51 min).[21] In the WOMAN trial, treatment delay might have been overestimated by considering the time of birth as the time of bleeding onset. We therefore subtracted a random number of minutes from the treatment delay using a uniform distribution with a constant minimum set at 0 and one maximum value of 30 min in the WOMAN dataset (post-hoc analysis). For each of the four maximum values in the CRASH-2 dataset and the single maximum value in the WOMAN dataset, we re-estimated the final model 100 times to obtain ranges for the time to treatment interaction (model 3). We ran all analyses in Stata/IC, version 14.2.

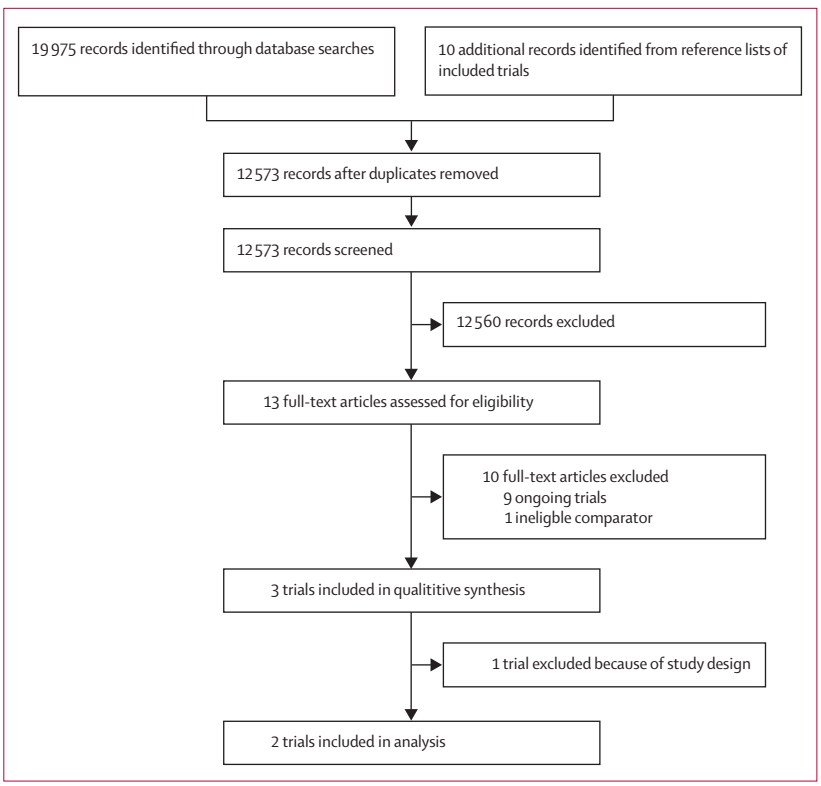

Figure 1: **Study selection**

Role of the funding source

The funders of the CRASH-2 and WOMAN trials had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Studies identified in our search are shown in figure 1. We found three completed[11,12,22] and nine ongoing trials,[21,23–27] (for three ongoing trials no published data were

available [EUCTR2015-002661-36-GB, NCT01060176, and NCT02936661]; appendix). All completed trials used tranexamic acid. The CRASH-2 trial[11] assessed the effects of tranexamic acid on death and vascular occlusive events in 20 211 bleeding trauma patients. The WOMAN trial[12] assessed the effects of tranexamic acid on death, hysterectomy, and other morbidities in 20 060 women with post-partum haemorrhage. The ATACAS trial[22] assessed the effects of tranexamic acid on death and thrombotic events in 4662 patients undergoing coronary artery surgery. Because all patients in the ATACAS trial were treated 30 min after induction of anaesthesia, we could not explore the effect of treatment delay in this trial. The included trials had low risk of bias for all domains (appendix).

We obtained individual patient-level data for 40 138 participants: 20 127 from the CRASH-2 trial and 20 011 from the WOMAN trial (table 1). The CRASH-2 trial participants were older than WOMAN trial participants. Of the 40 138 participants, 20 094 received tranexamic acid and 20 044 received placebo (table 2). Of the 3558 deaths, 1408 (40%) were due to bleeding, of which 884 (63%) occurred within 12 h of bleeding onset (appendix). In the WOMAN trial, where data on time to death were available, deaths from bleeding peaked at 2–3 h after bleeding onset in untreated women (figure 2). In the WOMAN trial, we excluded 109 (0·5%) patients with a treatment delay of more than 24 h (59 patients in the placebo group and 50 in the tranexamic acid group) on the basis of the WHO definition for primary post-partum haemorrhage.[28] We found no heterogeneity in the treatment effect between trials (model 1: interaction p=0·7243, appendix). Tranexamic acid significantly increased overall survival from bleeding (OR=1·20, 95% CI 1·08–1·33; p=0·001). We found similar results when we excluded from analysis the 2150 deaths from causes other than bleeding (data not shown).

The appendix shows the treatment benefits stratified by 60-min intervals of delay. With the exception of the first hour, effectiveness decreased with increasing treatment delay. Among patients who died from bleeding (appendix), we found that those who received treatment within the first hour were more often women and were younger with a higher proportion of penetrating injuries (for trauma patients). We found no heterogeneity in the interaction between treatment delay and the effect of tranexamic acid between trials (model 2: p=0·1363 for the triple interaction between the trial, tranexamic acid, and treatment delay with linear terms and p=0·3891 for the triple interaction between the trial, tranexamic acid, and treatment delay with squared terms). In model 3, treatment delay appeared to reduce the treatment benefit (p<0·0001 for the trend of increasing benefit with earlier

	CRASH-2 trial	WOMAN trial	Total
Number of patients randomised	20 127	20 011	40 138
Time to treatment (h)			
≤1	7452 (37·0%)	9572 (48·1%)	17 024 (42·5%)
1–3	6033 (30·0%)	5356 (26·9%)	11 389 (28·5%)
>3	6634 (33·0%)	4974 (25·0%)	11 608 (29·0%)
Missing or excluded data	8 (0·0%)	109 (0·5%)	117 (0·3%)
Mean (SD)	2·8 (2·1)	2·5 (3·4)	2·7 (2·9)
Median (IQR)	2·0 (1·0–4·0)	1·1 (0·5–3·0)	1·8 (0·8–4·0)
Age (years)			
≤25	6655 (33·1%)	6541 (32·7%)	13 196 (32·9%)
25–30	3417 (17·0%)	6707 (33·5%)	10 124 (25·2%)
30–35	2413 (12·0%)	4357 (21·8%)	6770 (16·9%)
>35	7640 (38·0%)	2399 (12·0%)	10 039 (25·0%)
Missing data	2 (0·0%)	7 (0·0%)	9 (0·0%)
Mean (SD)	34·6 (14·3)	28·5 (5·7)	31·5 (11·3)
Median (IQR)	30 (24–43)	28 (24–32)	29 (24–35)
Systolic blood pressure (mm Hg)			
≤75	3161 (15·7%)	1666 (8·3%)	4827 (12·0%)
75–90	6885 (34·3%)	5787 (28·9%)	12 672 (31·6%)
>90	10 052 (50·0%)	12 553 (62·8%)	22 605 (56·4%)
Missing data	29 (0·1%)	5 (0·0%)	34 (0·1%)
Mean (SD)	97·0 (27·9)	100·8 (22·7)	98·9 (25·5)
Median (IQR)	91 (80–110)	100 (90–110)	100 (87–110)

Table 1: **Baseline characteristics of patients in participating trials**

	CRASH-2 trial		WOMAN trial		Total	
	Tranexamic acid (n=10 060)	Placebo (n=10 067)	Tranexamic acid (n=10 034)	Placebo (n=9977)	Tranexamic acid (n=20 094)	Placebo (n=20 044)
Any cause of death	1463 (14·5%)	1613 (16·0%)	227 (2·3%)	255 (2·6%)	1690 (8·4%)	1868 (9·3%)
Death due to bleeding	489 (4·9%)	574 (5·7%)	155 (1·5%)	190 (1·9%)	644 (3·2%)	764 (3·8%)
Non-bleeding death	974 (9·7%)	1039 (10·3%)	72 (0·7%)	65 (0·7%)	1046 (5·2%)	1104 (5·5%)
Vascular occlusive events	168 (1·7%)	201 (2·0%)	31 (0·3%)	34 (0·3%)	199 (1·0%)	235 (1·2%)
Vascular death	33 (0·3%)	48 (0·5%)	10 (0·1%)	11 (0·1%)	43 (0·2%)	59 (0·3%)
Myocardial infarction*	35 (0·4%)	55 (0·5%)	2 (0·0%)	3 (0·0%)	37 (0·2%)	58 (0·3%)
Stroke*	57 (0·6%)	66 (0·7%)	8 (0·1%)	6 (0·1%)	65 (0·3%)	72 (0·4%)
Pulmonary embolism*	72 (0·7%)	71 (0·7%)	17 (0·2%)	20 (0·2%)	89 (0·4%)	91 (0·5%)
Deep vein thrombosis*	40 (0·4%)	41 (0·4%)	3 (0·0%)	7 (0·1%)	43 (0·2%)	48 (0·2%)

*Includes both fatal and non-fatal events.

Table 2: **Deaths and vascular occlusive events by treatment allocation**

treatment, figure 3) after adjustment for age and systolic blood pressure. When given immediately, tranexamic acid significantly improved survival (OR=1·72, 95% CI 1·42–2·10; p<0·0001) but the benefit decreased with increasing delay in a non-linear association (p=0·0109 for the interaction between treatment group and treatment delay squared). We estimated the time at which the lower bound of the 95% CI crossed the null value to be 135 min, with no apparent treatment benefit observed at 180 min. From model 3, we estimated that the treatment benefit decreased by 10% for every 15 min of treatment delay (figure 4). We found the same results after exclusion of deaths from other causes (data not shown).

After applying a random correction of up to 60 min to treatment delay for patients in the CRASH-2 trial and a random subtraction of up to 30 min to treatment delay in the WOMAN trial (post-hoc analysis), the relative treatment benefit from immediate tranexamic acid treatment varied between 70% (OR 1·70, 95% CI 1·38–2·11) and 82% (1·82, 1·47–2·25), with an average of 77% (1·77, 95% CI 1·43–2·18; appendix). The timepoint at which tranexamic acid had no effect increased from 180 min to 200 min.

The risk of vascular occlusive events was higher in patients with traumatic bleeding than in those with post-partum haemorrhage. There was no increase in fatal vascular occlusive events with tranexamic acid (OR 0·73, 95% CI 0·49–1·09; p=0·1204), with no heterogeneity between trials (p=0·5956; appendix). There were fewer cases of myocardial infarction (mostly reported in CRASH-2) with tranexamic acid (OR=0·64, 95% CI 0·43–0·97; p=0·0371) but there was no significant reduction in other vascular occlusive events. Treatment delay did not modify the effect of tranexamic acid on vascular occlusive events even after correction for misclassification. Adjustment for age or systolic blood pressure did not influence the results.

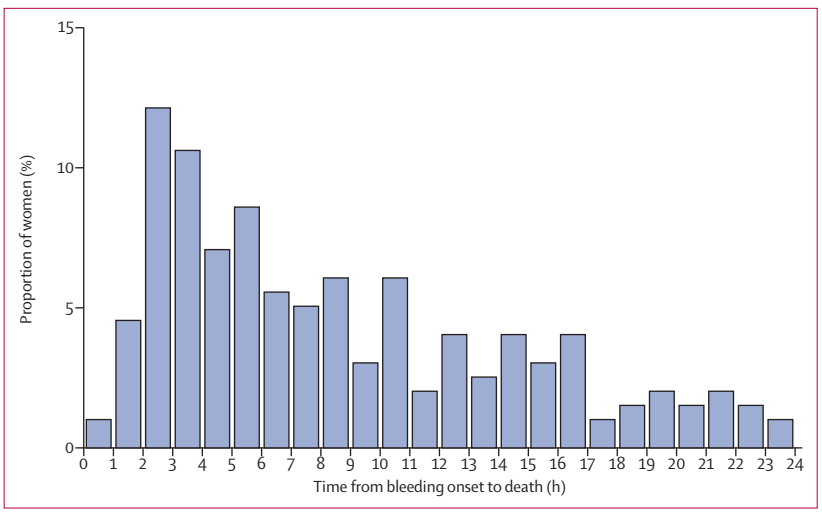

Figure 2: **Hours from onset of bleeding to death from bleeding among untreated women with post-partum haemorrhage**

Discussion

The principal findings of our individual patient-level data meta-analysis are that most deaths from bleeding occur on the day of onset and many occur within the first few hours. Deaths from post-partum haemorrhage peak at 2–3 h after childbirth. Tranexamic acid improves survival but treatment delay reduces the benefit. Every 15 min of treatment delay appears to decrease the benefit by about 10%, with no benefit after 3 h. We found no increase in vascular occlusive events with tranexamic acid.

Our study has various strengths and limitations. First, to reduce selection bias we excluded trials with fewer than 1000 patients. Small trials are underpowered to assess effects on death and there is an increased risk of selective reporting.[29] Second, time of death was only available for post-partum haemorrhage. However, the distribution of deaths by days since bleeding onset was similar in traumatic and post-partum bleeding, and studies show that deaths from traumatic bleeding also peak in the first few hours after injury.[30] Third, we assessed the effect of treatment delay on treatment effectiveness by use of logistic regression models with second-order polynomials to take into account the non-linearity of treatment effect. Because an on–off step function in treatment effectiveness is biologically implausible and highly unlikely, we used treatment delay as a continuous variable. To explore the interaction between treatment effect and time, we used all observations of patients treated within 24 h from bleeding onset and not only within 3 h. Although we found no statistical heterogeneity in the interaction between treatment delay and the effect of tranexamic acid between trials, whether the physiology of bleeding varies by cause is open to question. Treatment delay might be under-estimated in trauma, since many injuries are unwitnessed, and it might have been over-estimated in post-partum haemorrhage because time of birth was taken as the time of onset. Because of these uncertainties, we did sensitivity analyses with a range of plausible errors. Results of these analyses support the conclusion that prompt treatment is essential. Fourth, deaths due to bleeding and deaths from vascular occlusive events could have been misclassified.[11,12] Some deaths attributed to bleeding might have been due to thrombotic disseminated intravascular coagulation, especially those occurring several hours after onset. Although results adjusted for age and systolic blood pressure were similar, we cannot exclude the possibility that other unmeasured factors might have influenced the results. The large sample size—more than 40 000 patients with acute severe bleeding—provided a precise assessment of the effect of treatment delay with statistically significant results. All analyses were done on an intention-to-treat basis and missing data were negligible.

Our findings indicate that even a short treatment delay reduces the survival benefit from tranexamic acid. With the exception of the first hour, we found a clear trend of decreasing effectiveness with increasing treatment delay.

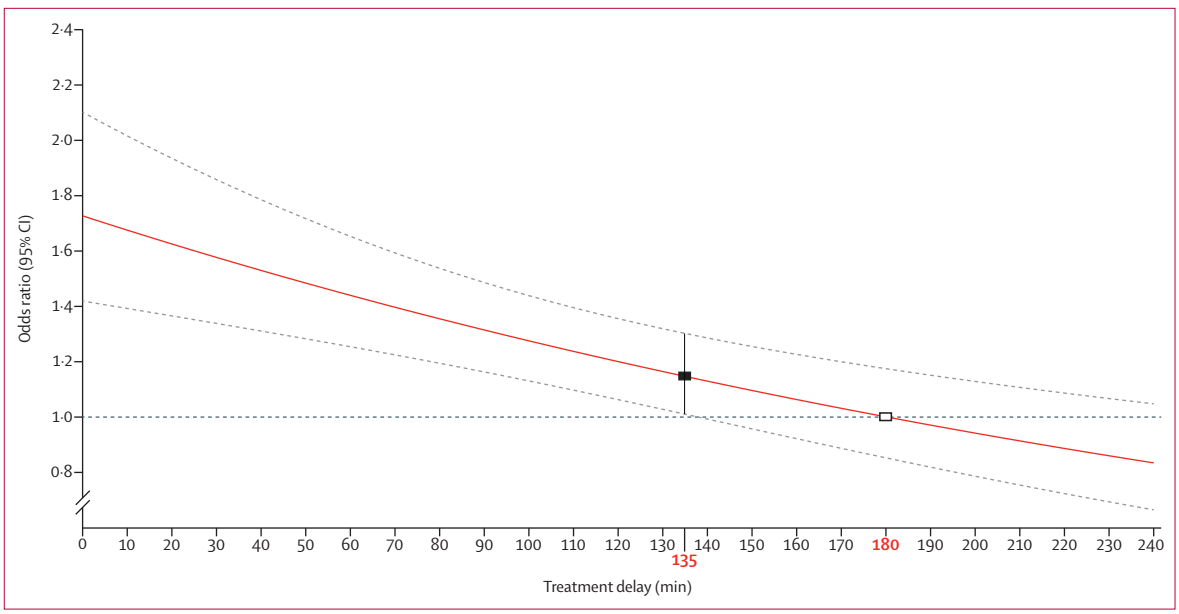

Figure 3: **Effect of treatment delay on treatment benefit (model 3)**
The red line shows the best fitted model for the association between the protective effect of tranexamic acid (odds ratio for not dying from bleeding) and duration of treatment delay in minutes (p_{slope}<0·0001). The grey lines are the lower and upper bounds of the 95% CI for this model. Estimates are derived from a logistic regression model of not dying from bleeding explained by the interaction of getting tranexamic acid and treatment delay (linear and squared terms) and adjusted for trial, age (5-year intervals), and systolic blood pressure (10-mm Hg intervals). The white square shows the timepoint at which the model estimates a null effect of tranexamic acid (a treatment delay of 180 min). The black square shows the timepoint at which the lower 95% CI model estimates a null effect of tranexamic acid (a treatment delay of 135 min).

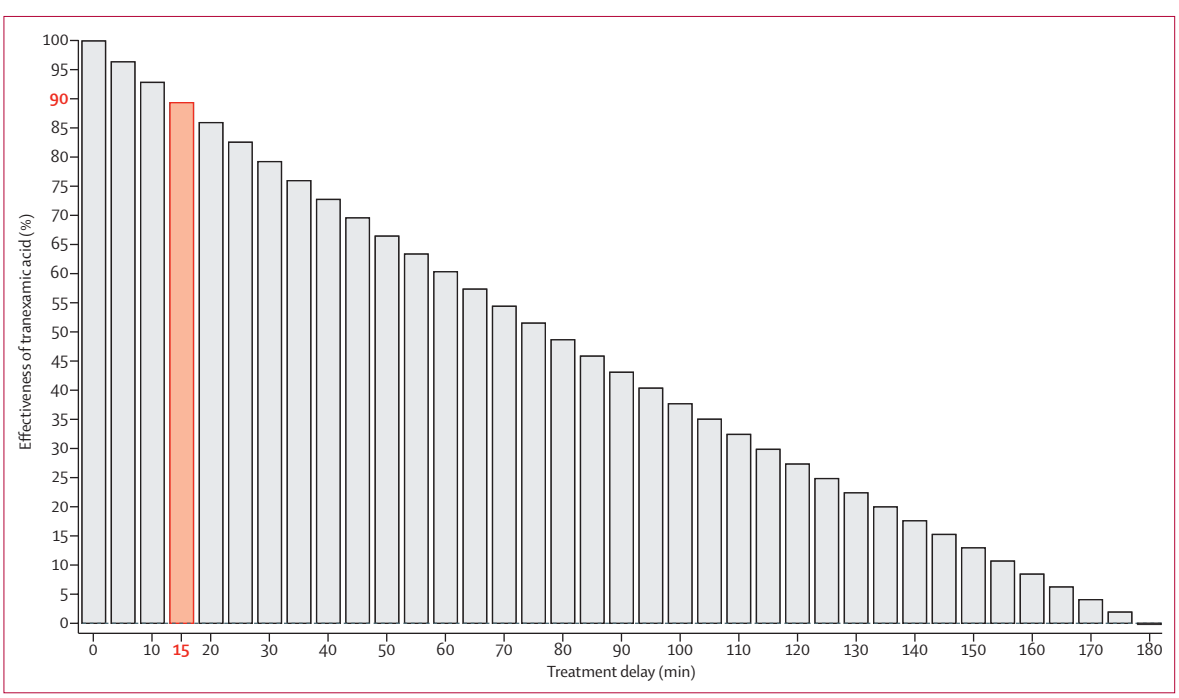

Figure 4: **Reduction in effectiveness of tranexamic acid with increasing treatment delay**
The bars represent the estimated treatment effectiveness (y-axis, estimated by [(OR at time $t-1$)/ (OR at $t=0-1$) × 100] in %) at 5-min intervals of treatment delay. The bar highlighted in red shows the estimated treatment effectiveness (90%) with a treatment delay of 15 min.

The apparently lower treatment effect within the first hour might be due to random variability or limitations in timing the onset of bleeding (appendix). Alternatively, a larger proportion of patients treated within an hour of bleeding onset might have unsurvivable haemorrhage.[30] Trauma patients treated within an hour of injury were more likely

to have penetrating injuries than those treated later (appendix). With regard to the decrease in treatment effectiveness with increasing delay, several hypotheses can be proposed. First, we should expect some time lag between administration of tranexamic acid and its effect on mortality. It is unlikely that deaths occurring very soon after tranexamic acid administration could have been prevented by tranexamic acid. However, their inclusion in the trial will bias (dilute) the treatment effect towards the null. Given the temporal distribution of deaths from bleeding shown in figure 2, the extent of this null bias would increase with increasing treatment delay. Second, the ability to form a clot depends on fibrinogen concentrations. In patients with trauma and post-partum haemorrhage, low serum fibrinogen is predictive of life threatening bleeding.[31,32] Fibrinogen falls rapidly in severe bleeding because of its consumption during clot formation. However, fibrinolysis and fibrinogenolysis would increase the consumption of fibrinogen. Early tranexamic acid treatment should protect fibrinogen stores and maintain the ability to form a stable fibrin clot. Indeed, we should consider tranexamic acid as an intervention to prevent rather than treat coagulopathy. Further research into the mechanism of action of tranexamic acid in acute severe bleeding should improve our understanding of the observed time to treatment interaction.

These findings have various implications for clinical care. Bleeding patients should receive antifibrinolytics as soon as possible for three reasons. First, most deaths from haemorrhage occur within hours of bleeding onset. By reducing bleeding, tranexamic acid has the potential to prevent the hypoxia and acidosis that accompanies severe bleeding, but it must be given before tissue damage is irreversible. Second, the benefit of tranexamic acid treatment appears to decrease with increasing treatment delay. Third, we found no evidence of adverse effects associated with tranexamic acid treatment, so it can be given safely as soon as bleeding is suspected. Given the importance of early treatment, time from bleeding onset to treatment should be audited with feedback provided to health-care professionals. National or regional quality improvement initiatives, with best practice benchmarking of time to treatment, might improve survival.

We found nine ongoing trials of antifibrinolytics in acute severe bleeding. Two of these will provide additional data on the effect of treatment delay in severe extracranial bleeding. Because the data from these two trials will increase the number of participants by only 5%, it is unlikely that they will have a material effect on our conclusions. Nonetheless, ongoing trials should deepen our understanding of the safety and effectiveness of antifibrinolytics in traumatic and spontaneous intracranial bleeding, which are major causes of death and disability worldwide. Our review protocol also proposed an analysis of the extent to which the balance of benefits and harms of antifibrinolytic treatment vary with baseline risk. These results will be reported in a future publication.

Contributors

IR proposed the meta-analysis. AG-A, KK, and IR reviewed the scientific literature and wrote the study protocol. AG-A, DP-M, and IR were responsible for the statistical analysis plan, data analysis, data interpretation, and drafting. AG-A, DP-M, KK, HS, F-XA, and IR contributed to the interpretation of the results, critical revision of the manuscript, and approved the final version. AG-A, DP-M, KK, HS, F-XA, and IR agreed to be accountable for all aspects of the work.

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Declaration of interests

We declare no competing interests.

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Comparison of Fentanyl and Morphine in the Prehospital Treatment of Ischemic Type Chest Pain

Erin R. Weldon, MD, FRCPC(EM), Robert E. Ariano, PharmD, BCPS, FCCM, Robert A. Grierson, MD, FRCPC(EM)

Abstract

In the treatment of acute coronary syndromes, reduction of sympathetic stress and catecholamine release is an important therapeutic goal. One method used to achieve this goal is pain reduction through the systemic administration of analgesia. Historically, morphine has been the analgesic of choice in ischemic cardiac pain. This randomized double-blind controlled trial seeks to prove the utility of fentanyl as an alternate first-line analgesic for ischemic-type chest pain in the prehospital setting. Successive patients who were treated for suspected ischemic chest pain in the emergency medical services system were considered eligible. Once chest pain was confirmed, patients received oxygen, aspirin, and nitroglycerin therapy. If the ischemic-type chest pain continued the patient was randomized in a double-blinded fashion to treatment with either morphine or fentanyl. Pain scale scores, necessity for additional dosing, and rate of adverse events between the groups were assessed every 5 minutes and were compared using t-testing, Fisher's Exact test, or Analysis of Variance (ANOVA) where appropriate. The primary outcome of the study was incidence of hypotension and the secondary outcome was pain reduction as measured by the visual analog score and numeric rating score. A total of 207 patients were randomized with 187 patients included in the final analysis. Of the 187 patients, 99 were in the morphine group and 88 in the fentanyl group. No statistically significant difference between the two groups with respect to hypotension was found (morphine 5.1% vs. fentanyl 0%, $p = 0.06$). Baseline characteristics, necessity for additional dosing, and other adverse events between the two groups were not statistically different. There were no significant differences between the changes in visual analog scores and numeric rating scale scores for pain between the two groups ($p = 0.16$ and $p = 0.15$, respectively). This study supports that fentanyl and morphine are comparable in providing analgesia for ischemic-type chest pain. Fentanyl appears to be a safe and effective alternative to morphine for the management of chest pain in the prehospital setting. **Key words:** chest pain; prehospital; morphine; fentanyl; acute pain

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Introduction

Ischemic-type chest pain is the most common chief complaint resulting in transport to hospital.[1,2] Currently, both fentanyl and/or morphine may be carried by EMS systems with morphine being predominantly used to treat suspected ischemic-type chest pain. Given the large patient volume, there are operational and patient safety-related advantages of utilizing a single narcotic agent.

In acute coronary syndromes (ACS), sympathetic stress and catecholamine release is associated with myocardial irritability, arrhythmia, and infarct size.[3] As a result, analgesia is an important therapeutic goal, which is achieved with either fentanyl or morphine. Historically morphine has been the analgesic of choice in ischemic cardiac pain.[4] Morphine is endorsed by the American Heart Association in ST segment elevation myocardial infarction with a class 1 indication; however, its use in acute coronary syndromes may be associated with increased mortality.[5]

The modern era of cardiac care creates the demand for rapid diagnostic and treatment times involving all aspects of ACS care.[6] First medical contact to treatment is a well-established time for benchmarking, quality improvement, and most importantly patient outcomes. It follows that a rapid onset of action of any cardiac treatment including analgesia is ideal. Because of its immediate onset of action and lower histamine release, allowing for more hemodynamic stability, intravenous fentanyl may be a better option than morphine in the pre-hospital setting.[7]

The goal of this study was to evaluate the utility of fentanyl as a superior alternate first line analgesic for ischemic chest pain in the pre-hospital setting. We tested the hypothesis that the administration of fentanyl in this setting would result in a lower incidence of hypotension compared with morphine.

Methods

Case Identification

This was a prospective double-blind randomized controlled trial of morphine vs. fentanyl in the treatment

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of ischemic type chest pain in the pre-hospital setting. Successive patients aged 18 years or over, treated for ischemic type chest pain in the emergency medical services system in Winnipeg, Manitoba were screened for enrollment in the study. The Winnipeg Fire Paramedic Service is an urban EMS system providing care for a population of 708,400 and employs a two-tiered approach to 911 dispatch information of which ischemic type chest pain calls receive a combined basic life support (BLS) and advanced life support (ALS) provider response. Transport to hospital occurs via ambulance with both BLS and ALS providers attending to the patient. During the study the BLS provider assessed for eligibility and obtained consent while the ALS provider delivered the study drugs and collected clinical data.

In order to be eligible for participation, the patient was required to meet the following inclusion criteria: (1) typical ischemic type chest pain not relieved by oxygen, acetylsalicylic acid (ASA), and nitroglycerin; (2) initial systolic blood pressure greater than 100 mmHg; and (3) initial oxygen saturation greater than 95%. Electrocardiogram interpretation was not used for inclusion eligibility to allow for inclusion of a wide spectrum of acute coronary syndrome patients including those with acute myocardial infarction. Exclusion criteria was as follows: (1) patients under the age of 18; (2) known pregnancy; (3) cognitive impairment; (4) known allergy to either fentanyl or morphine; (5) traumatic injury; and (6) patients with evidence of right ventricular infarct identified by the presence of ST segment elevation in V4R on prehospital electrocardiogram.

Upon arrival of the ALS paramedic and once chest pain suggestive of myocardial ischemia was confirmed, patients received supplemental oxygen at four liters per minute via nasal prongs, chewable ASA 160 mg, and nitroglycerin spray 0.4 mg sublingually every five minutes to a maximum of three doses. This treatment sequence is per Winnipeg Fire and Paramedic prehospital chest pain protocol. A nitroglycerine patch 0.2 mg/hr was also applied. If the patient continued to have pain despite the aforementioned therapy and they met all inclusion criteria and no exclusion criteria, they were approached and consented for enrollment. Given that the study patient population was expected to be heterogeneous in terms of criticality, informed consent was obtained using a summary consent process. An initial brief written consent was obtained on scene followed by a complete consent document once transferred to hospital. The complete consent document was not refused by any patients.

Data Collection

A standardized data collection tool was initiated for all patients enrolled. The patients' demographic information including age, gender, estimated height, and weight as well as clinical findings including blood pressure, heart rate, respiratory rate, and pain scores were recorded. Adverse events were also documented. Specifically adverse events were defined as but not limited to apnea, severe respiratory depression (defined as desaturation below 90%), nausea, emesis, and decreased level of consciousness. Hypotension as an adverse event was defined as any episode of systolic blood pressure less than 90. Severe adverse events were deemed present if the patient required ventilation with bag valve mask or intubation, and/or if the narcotic reversal agent, naloxone was given for apnea.

A routine survey of ambulance patient care reports containing the Winnipeg Fire and Paramedic diagnosis code for chest pain or myocardial infarction was undertaken to identify eligible subjects who were not initially considered for the study.

Trial Medication

Study drugs were supplied in coded preloaded syringes by an outside agency pharmacy and were identical in appearance. Patients were randomized to double blind treatment according to A or B alternative:

A: 1 Patients less than 75 years of age and greater than 50 kg, an intravenous injection of 5 mg of morphine was given every 5 min as needed to a maximum of four injections.
A: 2 Patients greater than or equal to 75 years of age and/or less than or equal to 50 kg, an intravenous injection of 2.5 mg of morphine was given every 5 min as needed to a maximum of four injections.
B: 1 Patients less than 75 years of age and greater than 50 kg, an intravenous injection of 50 mcg of fentanyl was given every 5 min as needed to a maximum of four injections.
B: 2 Patients greater than or equal to 75 years of age and/or less than or equal to 50 kg, an intravenous injection of 25 mcg of fentanyl was given every 5 min as needed to a maximum of four injections.

Randomization occurred in a block design with four syringes per block. Each syringe contained either morphine or fentanyl mixed with normal saline to result in a total volume of 8 mL. An external pharmacy performed the reconstitutions, as well as randomizations and consecutive coding based on a computer generated randomization list. Each patient received an ordered numeric code and received the medication in the corresponding prepackaged syringe to ensure allocation concealment. Morphine was dosed at 2.5 mg per 1 mL and fentanyl at 25 mcg per 1 mL. For patients greater than or equal to 75 years and less than or equal to 50 kg, 1 mL increments were drawn up for total dosing. For patients greater than 50 kg and less

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than 75 years 2 mL increments were drawn up for total dosing.

Pain Assessment

A previously validated visual analogue scale (VAS) was used to assess pain relief.[8] Study parameters were recorded at baseline and at 2, 4, 6, 10, and 15 minutes after the administration of the study drug. Patients were also asked to rate their pain on a Numerical Rating Scale (NRS) where 0 was no pain and 10 was the most severe pain.

Outcome Measures

The primary outcome was the incidence of hypotension. Secondary outcomes were pain relief as measured by the visual analogue scale and numeric rating score as well as alteration in hemodynamic and respiratory status as measured by repeated vital signs. Adverse events previously defined were also recorded.

Ethics

The study received approval from The University of Manitoba Biomedical Research Ethics Board.

Statistical Methods

Subjective and objective clinical findings were categorized as discrete unordered variables. Descriptive statistics were used to summarize the data. Baseline differences between treatment groups were analyzed with a Student's t–test. The response variables were measured repeatedly over time and were analyzed using a repeated measurements analysis of variance (ANOVA) model. We estimated morphine would have a 10% adverse event rate for hypotension[4,9] and that it would drop to 1% with fentanyl. Using an alpha of 0.05 and a power of 80%, we anticipated that we would need approximately 96 patients in each arm for a total of 192 patients. As the incidence of hypotension is low with fentanyl, we hypothesized that it would have this advantage over morphine for chest pain. Studies have reported variable results on blood pressure with fentanyl, but it is generally around 1%. Fleischman et al.[15] reported only 2 cases of fentanyl-related hypotension in 363 patients (i.e., 0.6% incidence) receiving fentanyl for out-of-hospital analgesia[9]; while Thomas et al. reported an incidence of 1.9% in 213 patients.[15] Thus, for our sample size calculations, we estimated the incidence of hypotension to be approximately 1%. Analysis was per protocol and therefore was restricted to participants who fulfilled all aspects of eligibility, interventions, and outcome assessment.

RESULTS

Between February 13, 2005 and June 25, 2006, ALS Paramedics treated 1,264 patients for ischemic type chest pain in the Winnipeg Emergency Medical Services system. Upon review of all patient care reports, 1,057 patients were not eligible on the basis of: (1) patient refusal (12.5%); (2) lack of inclusion criteria (50.8%); (3) presence of exclusion criteria (7.5%); (4) no IV access (3.8%); (5) unable to consent (9.7%); and (6) other reasons (15.7%). The majority of patients in the category of "other reason" were excluded due to close proximity to a hospital; transport time less than 5 minutes (Figure 1).

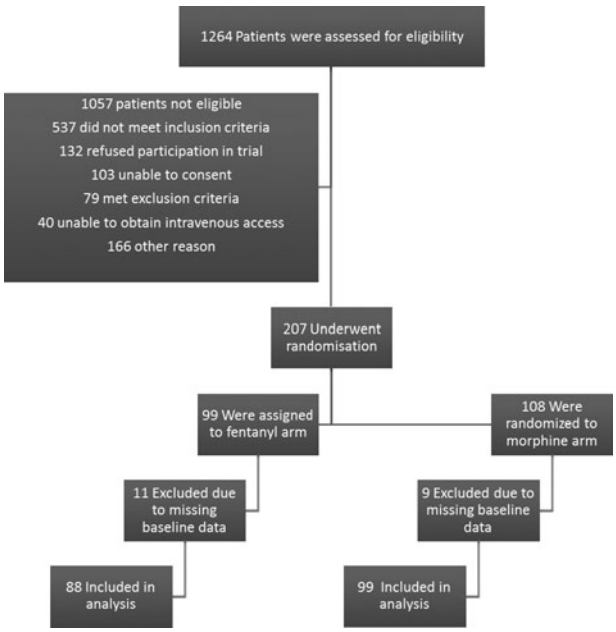

FIGURE 1. Overview of patient eligibility and enrollment.

During the study period 207 patients were randomized to either the fentanyl or morphine protocol. Of

TABLE 1. Baseline characteristics of patients

	Morphine	Fentanyl	*p*-value
Number of patients	99	88	
Age (years)	66.1 ± 15.8	64.5 ± 16.0	0.49
Weight (kg)	79.4 ± 19.6	78.43 ± 17.6	0.73
Range (kg)	36–150	40–140	
Height (cm)	170.3 ± 9.1	171.1 ± 8.6	0.53
Percent male	53%	53%	0.90
Size of dose received	1.7 ± 0.5	1.7 ± 0.5	0.84
Systolic blood pressure (mmHg)	141 ± 22	144 ± 21	0.33
Diastolic blood pressure (mmHg)	82 ± 14	83 ± 14	0.50
Heart rate	84 ± 23	87 ± 18	0.36
Respiratory rate	19 ± 4	20 ± 3	0.76
Numerical Rating Scale, NRS	5 ± 2	5 ± 2	0.89
Visual Analog Scale, VAS (cm)	4 ± 2	4 ± 2	0.76
Excluded - absence of baseline data	8	12	0.35

Statistical significance was analyzed by a 2-sided Student's t-test or Fisher's Exact where appropriate.

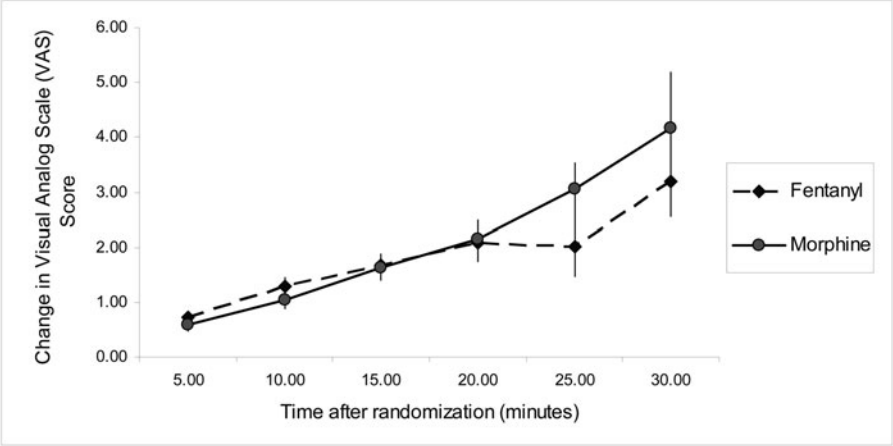

FIGURE 2. Progression of change in Visual Analog Scale (VAS) score. The greatest numerical but not statistical difference was found at 25 minutes ($p = 0.16$) by Kruskal-Wallis One-way Analysis of Variance.

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these patients, 20 patients (12 from fentanyl arm, 8 from morphine arm) were excluded due to lack of baseline data, leaving a study population of 187 patients.

The morphine and fentanyl groups did not differ significantly with respect to age, weight, baseline vital signs, or baseline pain scores (Table 1).

The change in overall VAS scores is shown in Figure 2. There was no significant difference between changes in VAS scores from baseline between either morphine or fentanyl ($p = 0.47$). Morphine appeared better 20 minutes after initiation of therapy, but this was not significant. In addition, there were no differences between changes in NRS, MAP, heart rate, or respiratory rate for either treatment arm (Figures 3–6).

From Table 2, it can be seen that there was no significant difference in the report of adverse events in both groups with nausea being the predominant side effect encountered. There were no cases of apnea in either treatment arm. All of the cases of hypotension were within the morphine arm (5.1% vs. 0%, $p = 0.06$). The necessity for additional narcotic doses was equivalent for both regimens (Table 3). There was a trend, however, toward more drug being required in the fentanyl arm in the first 5 to 9 minutes from the initiation of study drug ($p = 0.08$).

DISCUSSION

The progress of modern cardiac care has resulted in emergency medical systems being held to strict time standards in the treatment of ischemic chest pain. Therapeutic interventions from first medical contact must be rapid in order to stay in pace with time to thrombolytic and percutaneous coronary intervention goals. The more rapid onset of fentanyl is consistent with the practice of reducing treatment times in modern prehospital ACS care. Historically, out of hospital pain management has been suboptimal,[10,11] which may be related to the slow onset of action of morphine.

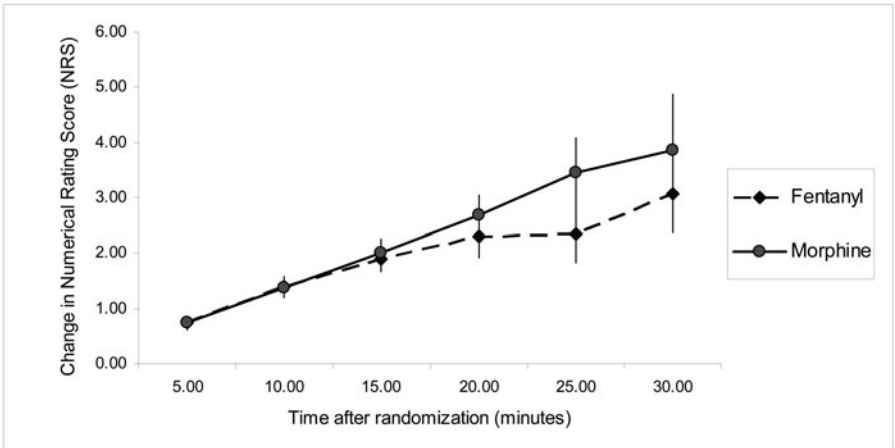

FIGURE 3. Progression of change in the Numerical Rating Scale (NRS) score. The greatest numerical but not statistical difference was found at 25 minutes ($p = 0.15$) by Kruskal-Wallis One-way Analysis of Variance.

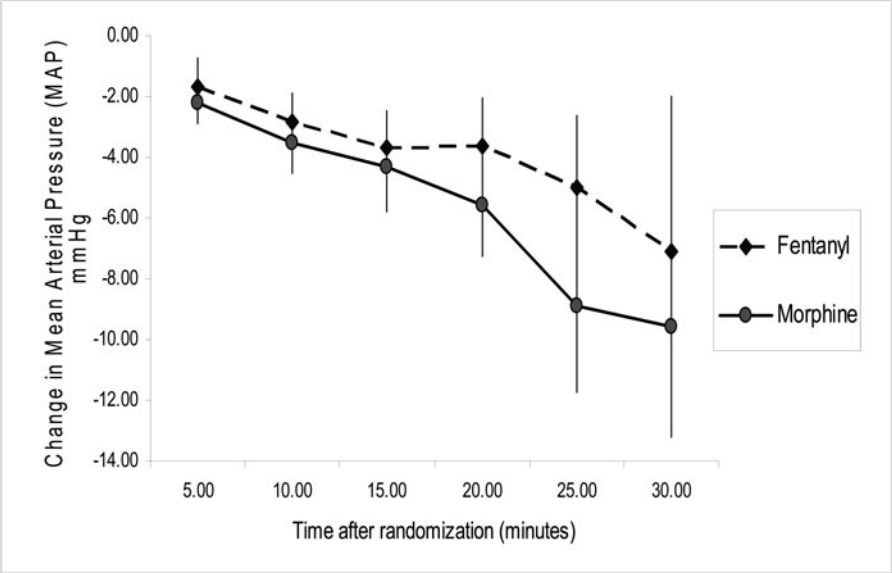

FIGURE 4. Progression of change in Mean Arterial Pressure (MAP). The greatest numerical but not statistical difference was found at 20 minutes ($p = 0.48$) by Kruskal-Wallis One-way Analysis of Variance.

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Fentanyl is an ideal agent in this setting with an immediate onset of action and less side effects than the traditionally used morphine. Although a similar study was performed using alfentanil,[12] and multiple studies have addressed the utility of fentanyl in an undifferentiated prehospital population,[7,13–15] to the best of our knowledge this is the first study to compare intravenous morphine and intravenous fentanyl in the setting of prehospital ischemic-type chest pain.

In many emergency medical systems, fentanyl is commonly used to treat traumatic pain, while morphine has been the historic choice for ischemic-type chest pain likely due its inclusion in the American Heart Association guidelines for Acute Coronary Syndromes.[16] The rationale for this assignment of opiates is poorly supported and there is evidence that the use of morphine in the setting of ACS may increase infarct size and result in increased mortality.[5] Morphine's hemodynamic effects are theorized to influence myocardial oxygen consumption resulting in deleterious effects on outcome in ACS.[5] The histamine-releasing properties of opiates from mast cells appear to be distinct from that of known opiate receptors.[17] Although fentanyl has a similar pharmacokinetic profile as morphine, it is the preferred agent if hemodynamic instability results from morphine's histamine-releasing properties.[18] As shown in Table 2, our findings support this, as 5 patients who had received morphine had sustained episodes of hypotension whereas no fentanyl patient had evidence of hypotension. Although these values are not statistically significant, the trend does support the belief

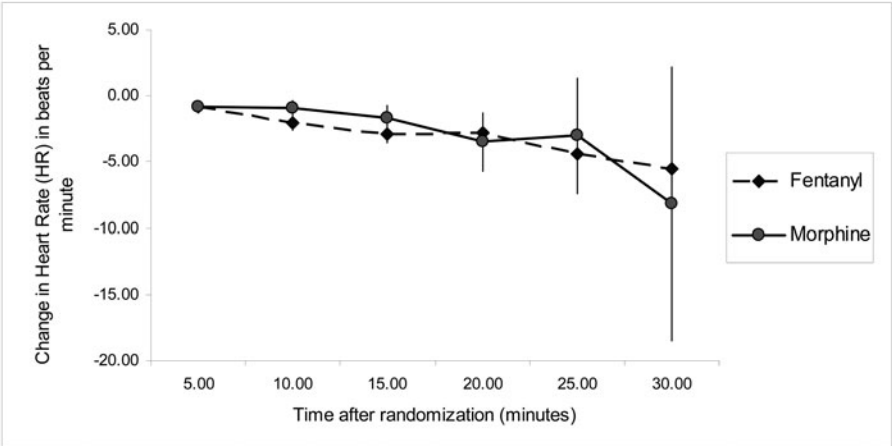

FIGURE 5. Progression of change in heart rate. The greatest numerical but not statistical difference was found at 15 minutes ($p = 0.09$) by Kruskal-Wallis One-way Analysis of Variance.

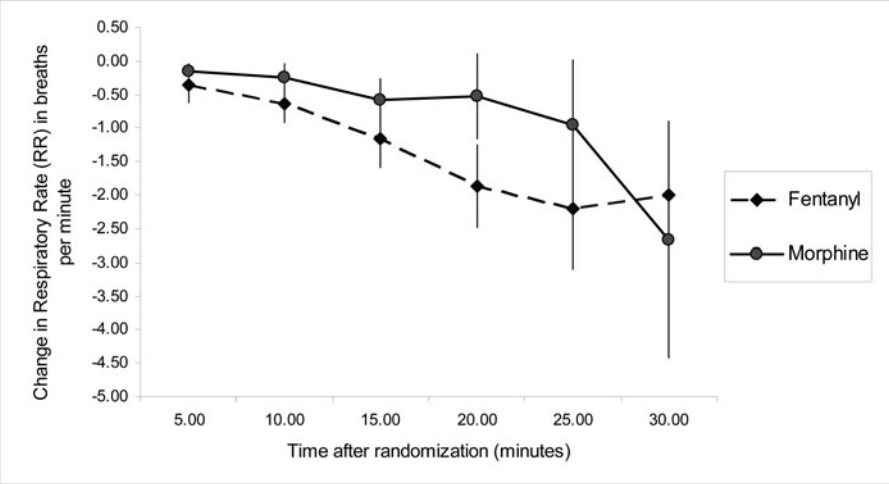

FIGURE 6. Progression of change in respiratory rate. The greatest numerical but not statistical difference was found at 20 minutes ($p = 0.13$) by Kruskal-Wallis One-way Analysis of Variance.

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that fentanyl is a more hemodynamically stable analgesic option. The avoidance of hypotension in ischemic chest pain patients is a major therapeutic goal.

In addition to blood pressure considerations, respiratory depression is often of concern in the administration of opioid analgesia. No patient in this study sustained any episodes of apnea and there was no statistical difference in respiratory rate reduction between the two groups as outlined in Table 4.

*A prio*r study performed in Helsinki comparing the narcotic alfentanil, which is similar to fentanyl, to morphine,[12] found similar results to our own. More specifically, morphine was as effective as alfentanil with respect to a reduction in pain scores and adverse effects.[4] A more similar and recent retrospective study in 355 patients also found comparable results when morphine and fentanyl were examined directly in a countywide EMS program for out-of-hospital analgesia.[15] A decrease in pain scores and adverse effects from either narcotic were found to be similar, however, their study design was limited by being a retrospective, before- and after-comparison.

There are advantages operationally, to utilizing a single narcotic for EMS services. The streamlining of narcotic delivery allows for reduced costs associated with tracking and storage and the potential for a reduction of divergence. Paramedic familiarity with a single agent improves accuracy of delivery, and reduces the potential for medication error.

A single opiate analgesic that has a rapid onset, is easily titrated and that can be delivered via many routes is desirable. Fentanyl meets all of these criteria and in addition is administrable via the intranasal route. The intranasal route of administration is invaluable in patient populations where initiating an intravenous line may not be desirable such as the pediatric and palliative care population.

LIMITATIONS

The population included in this study, was a heterogeneous chest pain population. Patients did not require definitive EKG evidence of infarct or ischemia but did require symptoms consistent with ischemic chest pain as opposed to chest pain related to other pathologic processes. We believe that this represents a

TABLE 2. Comparison of adverse events at any time point after the dose out to 30 minutes.

	Morphine (99)	Fentanyl (88)	*p*-value
Nausea	18.2% (18)	12.5% (11)	0.32
Apnea	0%	0%	1.00
Emesis	2.0% (2)	1.1% (1)	1.00
Requirement for dimenhydrinate	9.1% (9)	8.0% (7)	0.80
Hypotension (SBP < 90 mmHg)	5.1% (5)	0%	0.06

Statistical significance was analyzed by a 2-sided Fisher's Exact.

TABLE 3. Necessity for an additional dose of narcotic by treatment arm.

Time interval	Morphine (212*)	Fentanyl (195*)	*p*-value
1–4 mins	29%	26%	1.00
5–9 mins	76%	92%	0.08
10–14 mins	80%	71%	1.00
15–19 mins	51%	71%	0.79
20–24 mins	45%	76%	0.55
25–30 mins	57%	25%	1.00

Statistical significance was analyzed by a 2-sided Fisher's Exact.
*the denominator here is for the total number of patients within all the assessment periods (i.e. number of events assessed at 1–4 min, 5–9 min, etc.).

TABLE 4. Adverse events

Monitoring adverse parameter:	Fentanyl (mean ± SD)	Morphine (mean ± SD)	Between narcotics	Reduction over time overall
Heart Rate reduction	–5.5 ± 6.7 by 30 min	–8.1 ± 27.3 by 30 min	$p = 0.81$	$p = 0.23$
Respiratory Rate reduction	–2.0 ± 2.8 by 30 min	–2.7 ± 4.3 by 30 min	$p = 0.74$	$p = 0.52$
Mean Arterial Pressure reduction	–7.1 + 17.0 by 30 min	–9.6 + 8.0 by 30 min	$p = 0.87$	$p = 0.04$

Mean = the Least Squares mean as calculated by the ANOVA; SD = standard deviation.

real world approach to prehospital analgesia and supports the generalizability of our results to other EMS systems

A limitation of this study was the exclusion of patients who lacked baseline data, which resulted in an available case analysis as opposed to intention to treat. Imputation of data would require multiple assumptions in particular because the majority of the data is continuous and outcomes were measured as changes from baseline. Although exclusions are always a concern it is important to note that the rate of exclusion was no different between study arms (Table 1).

During the study 1264 chest pain patients were screened for enrollment and 1,057 did not meet inclusion criteria or did meet inclusion criteria but were not enrolled for logistical or other reasons. The low enrollment number may affect external validity of the study results; however, these were unavoidable within our current design but are an important consideration for future studies

The EMS system where the study was conducted is an urban centre with off-line medical control. The results may not be applicable to systems with other modes of medical control. We do believe the results may be relevant to other settings including rural patient populations and potentially the in-hospital patient population.

A final limitation would be the lack of hospital outcome data for the presence or absence of adverse events.

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Conclusion

Fentanyl appears to be a safe and effective alternative to morphine for the management of chest pain in the prehospital setting. This study demonstrates that fentanyl and morphine are comparable in providing analgesia for ischemic type chest pain in the prehospital setting.

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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

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Aims The use of opioids is recommended for pain relief in patients with myocardial infarction (MI) but may delay antiplatelet agent absorption, potentially leading to decreased treatment efficacy.

Methods and results In-hospital complications (death, non-fatal re-MI, stroke, stent thrombosis, and bleeding) and 1-year survival according to pre-hospital morphine use were assessed in 2438 ST-elevation MI (STEMI) patients from the French Registry of Acute ST-elevation and non-ST-elevation Myocardial Infarction (FAST-MI) 2010. The analyses were replicated in the 1726 STEMI patients of the FAST-MI 2005 cohort, in which polymorphisms of CYP2C19 and ABCB1 had been assessed. Specific subgroup analyses taking into account these genetic polymorphisms were performed in patients pre-treated with thienopyridines. The 453 patients (19%) receiving morphine pre-hospital were younger, more often male, with a lower GRACE score and higher chest pain levels. After adjustment for baseline differences, in-hospital complications and 1-year survival (hazard ratio = 0.69; 95% confidence interval: 0.35–1.37) were not increased according to pre-hospital morphine use. After propensity score matching, 1-year survival according to pre-hospital morphine was also similar. Consistent results were found in the replication cohort, including in those receiving pre-hospital thienopyridines and whatever the genetic polymorphisms of CYP2C19 and ABCB1.

Conclusion In two independent everyday-life cohorts, pre-hospital morphine use in STEMI patients was not associated with worse in-hospital complications and 1-year mortality.

Clinical trial registration Clinicaltrials.gov identifier: NCT00673036 (FAST-MI 2005); NCT01237418 (FAST-MI 2010).

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Keywords Acute myocardial infarction • Morphine • Opioids • ST-elevation myocardial infarction

Introduction

The use of opioids is recommended for pain relief, breathlessness, and anxiety in patients with acute myocardial infarction (AMI), although data from randomized controlled trials documenting its benefit or safety on hard outcomes are completely lacking.[1,2] Beyond its analgesic benefit *per se*, the use of opioids appears justified because pain is associated with sympathetic activation that causes vasoconstriction and increased cardiac workload.[2]

In heathy volunteers, however, recent data have demonstrated a drug–drug interaction between morphine and clopidogrel: concomitant injection of morphine slows clopidogrel absorption, decreases plasma levels of its active metabolite, retards, and diminishes its pharmacologic effects, a mechanism which could lead to treatment failure at the acute stage of MI.[3] Likewise, in ST-elevation myocardial infarction (STEMI) patients, inhibition of platelet reactivity by prasugrel and ticagrelor is delayed when morphine is co-administered.[4] Recently, the Administration of Ticagrelor in the cathLab or in the Ambulance for New ST elevation myocardial Infarction to open the Coronary artery (ATLANTIC) trial showed more frequent ST-segment resolution before percutaneous coronary intervention (PCI) in patients treated with ticagrelor in the ambulance when they did not receive pre-hospital morphine, whereas no such effect was observed in morphine-treated patients; there was no interaction between morphine use and infarct-related artery patency, however.[5]

The aim of this study was to assess the correlates of pre-hospital morphine use, and its relationship with clinical outcomes, in STEMI patients from the French Registry of Acute ST-elevation and non-ST-elevation Myocardial Infarction (FAST-MI) 2010. Consistency of the results was assessed by replicating the analyses in STEMI patients from the FAST-MI 2005 registry. In this latter cohort, special consideration was given to the patients who had been pre-treated with clopidogrel, according to genetic polymorphisms of ABCB1 and CYP2C19 enzymes, which are involved in clopidogrel absorption and metabolism.[6,7]

Methods

Primary analysis

For the main analysis, we selected patients with STEMI or left bundle branch block (LBBB) from FAST-MI 2010, the methodology of which has been previously described in detail.[8,9] Briefly, the primary objective was to evaluate practices for MI management in 'real life' and to measure their association with medium- and long-term outcomes in patients admitted to intensive care units (ICUs) with AMI. This registry results from a prospective multicentre (213 centres) study, including 4169 patients, recruited consecutively from ICUs over a period of 1 month, with a possible extension of recruitment up to one additional month. Participation in the study was offered to all French institutions, university teaching hospitals, general and regional hospitals, and private clinics with ICUs in the capacity to receive acute coronary syndrome (ACS) emergencies, and 76% participated.

We included men or women aged over 18 years, admitted within 48 h after symptom onset for an AMI characterized by the elevation of troponin or creatine phosphokinase myocardial band associated with at least one of the following elements—symptoms compatible with myocardial ischaemia, new pathological Q waves, ST-T changes compatible with myocardial ischaemia—and who agreed to take part in the study. For the present study, only patients presenting with persistent ST-elevation, presumed new Q waves, or presumed new LBBB were included.

The main exclusion criteria were (i) iatrogenic MI, defined as MI occurring within 48 h of a therapeutic procedure (bypass surgery, coronary angioplasty, or any other medical or surgical intervention); (ii) ACS diagnosis invalidated in favour of another diagnosis; and (iii) patients with unstable angina and no increase in cardiac biomarkers.

The registry was conducted in compliance with Good Clinical Practice guidelines, French law, and the French data protection law. The protocol was reviewed and approved by the Committee for the Protection of Human Subjects of Saint-Louis University Hospital, and the data file of FAST-MI was declared to the Commission Nationale Informatique et Liberté. All patients gave informed consent for their participation in the study. Clinicaltrials.gov identifier: NCT01237418.

Baseline characteristics (demographics, risk factors, and medical history) were collected prospectively. All data were recorded on computerized case record forms by dedicated research technicians sent in each of the centres at least once a week. In-hospital complications (recurrent MI, stent thrombosis, bleeding, or transfusion) were collected. Recurrent MI was defined as recurrence of clinical symptoms or occurrence of ECG changes accompanied by a recurrent increase of cardiac markers. Stent thrombosis was defined as definite or probable according to the Academic Research Consortium definition.[10] Bleeding was classified as major or minor according to the Thrombolysis in Myocardial Infarction (TIMI) criteria.[11] Follow-up data were collected through contacts with the attending physicians, the patients, or their family. If missing, vital status was assessed from the civil registries of the patients' birthplaces. One-year follow-up was 99% complete.

Replication analysis

For assessing the robustness of the results, we repeated the analysis in patients ($n = 1726$) with STEMI or LBBB in the FAST-MI 2005 registry, which had been carried out 5 years before, using a similar methodology, and in which polymorphisms of CYP2C19 and ABCB1 had been assessed in 66% of the patients.[6,12,13] Clinicaltrials.gov identifier: NCT00673036. In the 2005 registry, the only thienopyridine used was clopidogrel, and fewer patients had undergone primary PCI. The set of variables collected in 2005 was essentially similar to that collected in 2010, but some variables of interest, in particular stent thrombosis, had not been recorded in 2005.

Genetic testing in the FAST-MI 2005 cohort

Genomic DNA was extracted from whole-blood specimens with the use of a purifier (the MagNA Pure Compact Instrument, Roche) according to the manufacturer's recommendations. Genotyping for *CYP2C19* and *ABCB1* was performed with the use of an oligonucleotide ligation assay (SNPlex, Applied Biosystems) after initial amplification by means of a polymerase chain-reaction assay involving two primers for the major variant alleles *CYP2C19*2* (rs4244285), *CYP2C19*3* (rs4986893), and *ABCB1* (rs1045642). Genotyping for known variants of *CYP2C19* with functional importance—*CYP2C19*4* (rs28399504), *CYP2C19*5*,

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*CYP2C19*17* (rs12248560)—was performed with the use of an allelic discrimination assay (Custom TaqMan) and a detection system (ABI prism 7900HT Sequence Detection System, Applied Biosystems). Base numbering and allele definitions follow the nomenclature of the Human Cytochrome P450 (*CYP*) Allele Nomenclature Committee (www.cypalleles.ki.se).

Statistical analysis

Continuous variables are reported as means and standard deviations (SDs) or medians and interquartile ranges (IQRs), when appropriate. Discrete variables are described as counts and percentages. Comparisons were made with χ^2 or Fisher's exact tests for discrete variables, and by unpaired *t* tests, Wilcoxon sign-rank tests, Mann–Whitney tests, or one-way analyses of variance for continuous variables. Backward binary logistic regression analysis, using pre-hospital morphine use, baseline characteristics, and therapeutic management as covariates, was used to determine independent correlates of in-hospital complications. In addition, a propensity score for getting morphine was calculated using multiple logistic regression (using baseline characteristics of the patients and concomitant pre-hospital medications received) and used to build two cohorts of patients (388 patients each) matched on the propensity score, using a greedy matching procedure; the *C*-statistic for the propensity score was 0.87, and the Hosmer–Lemeshow test was not significant ($P = 0.32$). The differences between the two matched cohorts were assessed by calculating the absolute value of standardized differences, and were always $\leq$10%. The matched population would give an 80% power to detect an absolute 6% increase in 1-year mortality in the morphine group, based upon an expected 7% mortality in the control group. Survival curves were estimated using the Kaplan–Meier estimation and compared using log-rank tests. Multivariate analyses of predictors of in-hospital endpoints were made by using backward, stepwise multiple logistic regressions. Correlates of survival were determined using a multivariate backward stepwise Cox analysis, using baseline characteristics and early management data as covariates. Statistical analyses were performed using IBM SPSS 20.0 (IBM SPSS Inc.) and NCSS 9 (NCSS, LLC. Kaysville, UT, USA). For all analyses, a two-sided *P* value of <0.05 was considered to be statistically significant.

Results

Main analysis in FAST-MI 2010

Baseline characteristics and clinical presentation

Of the 4169 patients included, 2438 had STEMI or LBBB, of whom 453 (19%) received morphine in the pre-hospital setting. Patients receiving morphine were younger, more often male, with a lower cardiovascular risk profile, and a lower early GRACE score (136 $\pm$ 31 vs. 145 $\pm$ 35, $P < 0.001$). Their past medical history, however, was not significantly different (*Table 1*).

Morphine was used in similar proportions of patients during the day (7:00 to 22:59) compared with night (23:00 to 6:59): 19 vs. 17%, $P = 0.44$, but more frequently during weekends compared with the rest of the week (22 vs. 18%, $P = 0.02$).

Finally, morphine was more often used in patients calling earlier, with typical chest pain, more severe chest pain, anterior MI, and in patients with lower heart rate and lower Killip class at presentation (*Table 2*). There was an inverse relationship between chest pain intensity and age: the proportion of patients with a pain score $\geq$7 decreased from 53% under 60 years of age to 47% for age 60–74 and 38% in patients 75 years of age or older ($P = 0.008$).

Pre- and in-hospital management

Pre-hospital morphine use was linked to initial pathways (*Table 2*). All patients who received morphine pre-hospital were managed by mobile ICU, with morphine prescribed by the physicians on board the ambulances. In these patients, time from ECG to primary PCI was shorter, and the use of antiplatelet and anticoagulant therapy was higher compared with patients without morphine. Metoclopramide, an antiemetic agent, was used more often in patients given morphine.

The percentage of patients admitted to centres with catheterization laboratories was higher when morphine was used (93 vs. 68%, $P < 0.001$), as was the use of primary PCI (90 vs. 77%, $P < 0.001$).

In-hospital evolution and 1-year clinical outcomes

Pre-hospital use of morphine was associated with a decrease in heart rate (-3.4 ± 18.8 vs. $+1.5 \pm 18.9$ b.p.m., $P < 0.001$) but no change in systolic blood pressure ($+13 \pm 28$ vs. $+14 \pm 28$ mmHg, $P = 0.69$), while change in Killip class was similar in patients with or without morphine (*Tables 2* and *3*). In patients who underwent coronary angiography, the rate of TIMI 2 or 3 flow prior to PCI was similar in patients with (41%) or without (41%) pre-hospital use of morphine. In those given morphine, TIMI 2 or 3 flow as found as frequently in those receiving metoclopramide (43%) or not (41%).

After adjustment, in-hospital mortality and most in-hospital complications did not differ according to pre-hospital morphine use; the rate of non-fatal recurrent MI, however, was higher in patients pre-treated with morphine (1.8 vs. 0.7%, $P = 0.03$; *Table 3*).

At 1 year, crude mortality rates were lower in patients with morphine (3.3%) vs. without morphine (8.7%). However, pre-hospital use of morphine was not an independent correlate of lower mortality (adjusted hazard ratio (HR) = 0.69; 95% confidence interval (CI): 0.35–1.37, $P = 0.29$) (*Figure 1*).

Analyses restricted to only those patients having been transported by emergency medical services yielded similar results (data not shown).

Propensity score-matched cohorts

Two propensity score-matched cohorts of 388 patients with similar baseline characteristics were built (see Supplementary material online, *Table S1*). Patients who received morphine had a greater decrease in heart rate and systolic blood pressure than those who did not. In-hospital death and 1-year mortality were similar in the patients who received compared with those who did not receive pre-hospital morphine (1.0 vs. 1.5% and 3.4 vs. 5.4%, respectively; Supplementary material online, *File S1*). Other in-hospital complications were not significantly different in both groups (including stent thrombosis 1.0 vs. 1.0% and non-fatal recurrent MI: 1.8 vs. 1.0%). Rate of TIMI 2 or 3 flow before PCI was lower in patients having received morphine (40 vs. 46%).

Subgroup having received thienopyridines in the pre-hospital setting

Among the 1108 patients in whom thienopyridines were administered pre-hospital (18% treated with prasugrel), 415 (37%) had also received morphine before hospital admission. As in the whole cohort, morphine-treated patients were younger and had a lower GRACE risk score (see Supplementary material online, *Table S2*). In-hospital complications were numerically less frequent in patients

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Table 1 Baseline characteristics: demographics, risk factors according to pre-hospital use of morphine

	Pre-hospital use of morphine (n = 453)	No pre-hospital use of morphine (n = 1985)	P-value
Age, mean ± SD, years	59.3 ± 13.9	64.2 ± 14.6	<0.001
Age ≥75 years, *n* (%)	65 (14)	547 (28)	<0.001
Female, *n* (%)	86 (19)	533 (27)	0.001
Body mass index, mean ± SD, kg/m^2	27.0 ± 4.3	26.7 ± 4.5	0.14
Risk factors, *n* (%)			
Hypertension	175 (39)	986 (50)	<0.001
Diabetes mellitus	56 (12)	333 (17)	0.02
Current smoking	239 (53)	762 (38)	<0.001
Dyslipidaemia[a]	178 (39)	807 (41)	0.59
Previous medical history, *n* (%)			
Myocardial infarction	50 (11)	210 (11)	0.78
Percutaneous coronary intervention	53 (12)	190 (10)	0.17
Coronary artery bypass grafting	21 (5)	100 (5)	0.72
Heart failure	6 (1)	56 (3)	0.07
Stroke	12 (3)	61 (3)	0.63
Peripheral artery disease	18 (4)	105 (5)	0.25
Chronic renal failure	6 (1)	58 (3)	0.06
Chronic obstructive lung disease	27 (6)	102 (5)	0.48
History of cancer	34 (7.5)	162 (8)	0.64
GRACE score	136 ± 31	145 ± 35	<0.001
Left ventricular ejection fraction, mean ± SD	50 ± 10	50 ± 11	0.98
Previous medications, *n* (%)			
Aspirin	72 (16)	314 (16)	0.97
Clopidogrel	28 (6)	142 (7)	0.46
Beta-blockers	72 (16)	379 (19)	0.11
Statins before	104 (23)	435 (22)	0.63
ACE-inhibitors or ARB	90 (20)	300 (30)	0.01
Chronic morphine	67 (3)	16 (3.5)	0.87

ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; GRACE, Global Registry of Acute Coronary Events.
[a]Included patients with previously documented diagnosis of hypercholesterolaemia be treated with diet or medication or new diagnosis made during this hospitalization with elevated total cholesterol >160 mg/dL; did not include elevated triglycerides.

receiving morphine, and in-hospital death was significantly lower. After adjustment on baseline characteristics and reperfusion therapy, however, there was no difference in hospital complication rates according to pre-hospital use of morphine (see Supplementary material online, *Table S3*). One-year mortality, however, was lower in patients receiving pre-hospital morphine (2.4 vs. 5.9%; adjusted HR = 0.45; 95% CI: 0.21–0.93, $P = 0.03$).

Replication cohort

Among the 3059 patients included in the FAST-MI 2005 registry, 1726 had STEMI of LBBB, of whom 279 (16%) had received morphine in the pre-hospital setting. Baseline characteristics differed between patients with or without pre-hospital morphine, with a pattern consistent with what was found in the 2010 cohort (see Supplementary material online, *Table S4*). Likewise, there was no evidence of increased complications in patients treated with morphine: in-hospital mortality was significantly lower in the morphine-treated population, but only a non-significant trend persisted after multivariate adjustment. Similar results were also observed in the population who had also received thienopyridines before hospital admission (see Supplementary material online, *Table S5*). One-year survival was also not significantly different in patients with vs. without pre-hospital morphine (whole cohort: adjusted HR 0.79, 0.46–1.36, $P = 0.39$; patients having received pre-hospital clopidogrel: adjusted HR 0.75, 0.18–3.10, $P = 0.70$).

Pre-hospital morphine use and outcomes according to genetic determinants of clopidogrel response in pre-hospital clopidogrel users

Genetic testing was available in 160 patients having received pre-hospital clopidogrel (*Table 4*). Variants of ABCB1, a genetic determinant of clopidogrel absorption, were correlated with initial infarct-related artery patency: TIMI 3 flow before PCI was observed in 37% of the patients with the wild-type allele (CC genotype), 23%

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Table 2 Clinical presentation and management according to pre-hospital use of morphine

	Pre-hospital morphine use ($n = 453$)	No pre-hospital morphine use ($n = 1985$)	*P*-value
Clinical presentation			
Typical chest pain, *n* (%)	424 (94)	1670 (84)	<0.001
Anterior MI, *n* (%)	211 (47)	716 (36)	<0.001
Systolic blood pressure (first medical contact) (mmHg), mean ± SD	140 ± 28	144 ± 28	0.007
Heart rate (first medical contact) (b.p.m.), mean ± SD	74 ± 19	79 ± 20	<0.001
Killips class ≥2, *n* (%)	25 (6)	184 (11)	0.001
Maximal ST elevation (mm), mean ± SD	3.7 ± 3.1 ($n = 307$)	3.0 ± 2.3 ($n = 1114$)	<0.001
Chest pain intensity (10-point scale), mean ± SD	7.1 ± 2.0 ($n = 257$)	5.8 ± 2.4 ($n = 631$)	<0.001
Pre-hospital management			
Initial pathway: mobile ICU, *n* (%)	453 (100)	1550 (78)	<0.001
Time delay from symptoms to ECG, median (IQR), min	79 (48; 126)	120 (67; 240)	<0.001
No. of patients	398	1535	
Time delay from ECG to primary PCI, median (IQR), min	91 (21; 2985)	121 (4; 3828)	<0.001
No. of patients	304	1088	
Aspirin, *n* (%)	428 (95)	779 (39)	<0.001
Clopidogrel, *n* (%)	328 (72)	1398 (30)	<0.001
Prasugrel, *n* (%)	88 (19)	107 (5)	<0.001
Low molecular weight heparin, *n* (%)	271 (40)	1639 (17)	<0.001
Fibrinolysis, *n* (%)	93 (20.5)	111 (6)	<0.001
Unfractionated heparin, *n* (%)	218 (48)	336 (17)	<0.001
Diuretics, *n* (%)	6 (1)	33 (2)	0.61
Amines, *n* (%)	7 (1.5)	5 (1)	0.63
Metoclopramide, *n* (%)	25 (5.5)	16 (0.8)	<0.001
Nitrates, *n* (%)	132 (29)	307 (15.5)	<0.001
In-hospital management, *n* (%)			
Percutaneous coronary intervention during first 24 h	375 (90)	1209 (77)	<0.001
Drug eluting stent	122 (28)	455 (27)	0.16
TIMI flow at first angiography (all patients)			
0/1	242 (59)	980 (59)	
2	55 (14)	197 (12)	0.68
3	111 (27) ($n = 406$)	494 (29) ($n = 1579$)	
TIMI flow 2/3 before PCI in patients with primary PCI	88 (28.5) ($n = 309$)	390 (33) ($n = 1173$)	0.11
TIMI flow 3 after PCI (all patients)	396 (93) ($n = 424$)	1409 (89) ($n = 1585$)	0.006
TIMI flow 3 after primary PCI	305 (94) ($n = 324$)	1080 (88.5) ($n = 1221$)	0.003

ICU, intensive care unit; IQR, interquartile ranges; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIMI, Thrombolysis In Myocardial Infarction.

of those with one variant allele (CT genotype) and 11% of those with two variant alleles (TT genotype) (P for trend = 0.01). The impact on 30-day (2.3, 2.3, and 3.6%) and 1-year death (4.7, 5.7, and 10.7%) rates, however, was not statistically significant. Neither TIMI 2 or 3 flow nor death rates differed in patients having or not received pre-hospital morphine, whatever the ABCB1 genotype. Likewise, although infarct-related artery patency was correlated with CYP2C19 loss-of-function variant alleles (P for trend = 0.049), no interaction was observed with pre-hospital morphine use; in particular, in patients without CYP2C19 loss of function variant alleles, TIMI 3 flow was found in 31% of those receiving morphine, compared with 27% in those without morphine ($P = 0.66$), and mortality was also not significantly different.

Discussion

The present data from a nationwide registry indicate that, in STEMI patients, pre-hospital morphine use was more frequent in younger patients with typical chest pain, calling earlier, and with more intense chest pain. Morphine use was associated with a decrease in heart rate, a potentially beneficial haemodynamic effect, and was not associated with higher rates of in-hospital complications or worse long-term survival. These results were observed both in the whole population of STEMI patients and in the population having received thienopyridines in the pre-hospital setting. The results were consistent after multivariate adjustments and propensity score matching and were confirmed by the replication analysis in a second cohort.

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Table 3 Evolution of haemodynamic parameters and in-hospital complications according to pre-hospital use of morphine

	Pre-hospital morphine use (n = 453)	No pre-hospital morphine use (n = 1985)	Adjusted odds ratio (95% CI)	P-value Crude *(adjusted)*
Systolic blood pressure change from first contact to admission (mmHg), mean ± SD	13 ± 28	14 ± 28	–	0.69
Heart rate change from first contact to admission (b.p.m.), mean ± SD	−3.4 ± 18.8	1.5 ± 18.9	–	<0.001
In-hospital complications, *n* (%)				
Death	6 (1.3)	88 (4.4)	0.48 (0.12–1.85)	0.002 (*0.29*)
Recurrent-MI	8 (1.8)	14 (0.7)	2.94 (1.17–7.37)	0.03 (*0.02*)
Death or recurrent MI	14 (3.1)	99 (5.0)	1.21 (0.59–2.50)	0.08 (*0.60*)
Stroke	1 (0.2)	12 (0.6)	0.49 (0.06–4.26)	0.31 (*0.52*)
Stent thrombosis	4 (0.9)	12 (0.6)	1.31 (0.36–4.74)	0.51 (*0.68*)
TIMI major bleeding	5 (1.1)	52 (2.6)	0.51 (0.20–1.32)	0.054 (*0.17*)
TIMI minor bleeding	13 (2.9)	58 (2.9)	0.99 (0.50–1.95)	0.95 (*0.98*)
Transfusion	6 (1.3)	58 (2.9)	0.68 (0.24–1.93)	0.055 (*0.47*)

MI, myocardial infarction; TIMI, Thrombolysis In Myocardial Infarction.

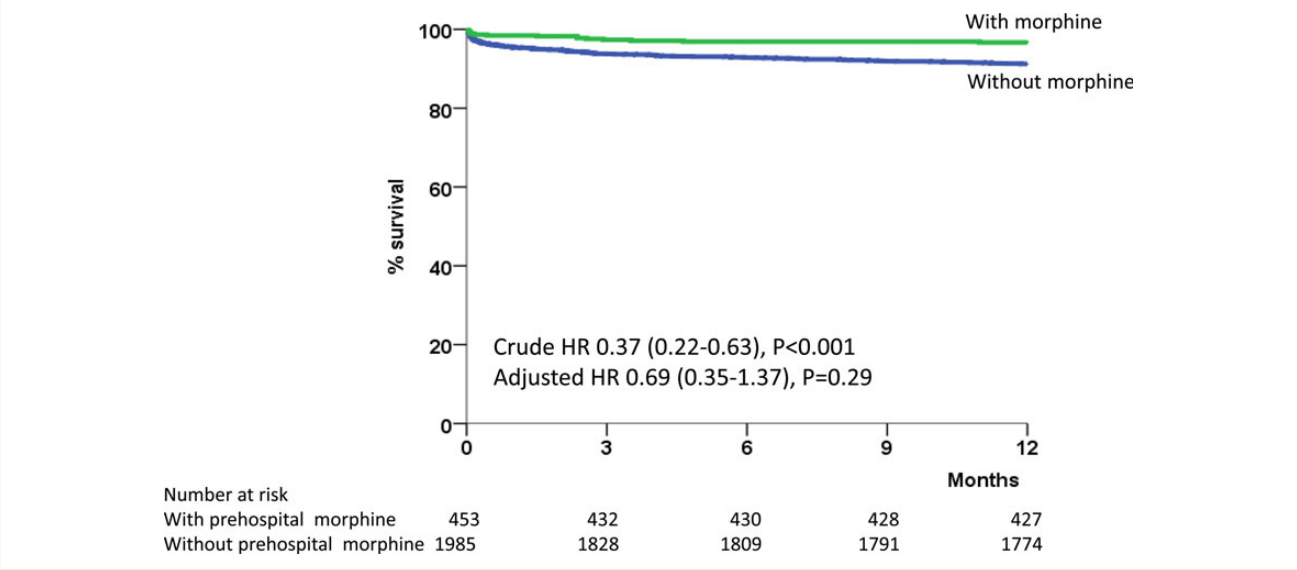

Figure 1 One-year survival according to pre-hospital morphine use. Kaplan–Meier curve for overall survival up to 1-year follow-up.

Exploratory genetic analyses also suggest that there was no deleterious impact of pre-hospital morphine use in patients treated with pre-hospital clopidogrel, whatever their genetic profile in terms of CYP2C19 (clopidogrel metabolism) and ABCB1 (clopidogrel absorption).

Pre-hospital morphine use is a class I recommendation for pain relief, breathlessness, and anxiety in patients presenting with AMI.[1,2] Despite these recommendations, and likely because of the absence of specific studies designed to assess its efficacy, morphine was used in a minority of patients in the pre-hospital setting (19%), even among those managed by emergency medical services (23%). Data on the use of opioids in the pre-hospital management of ACS patients are scarce. In the ATLANTIC trial,[5] ST resolution before primary PCI, an endpoint which was not collected in our study was observed more often after pre-hospital administration of ticagrelor when morphine had not been administered. However, it is noteworthy that in ATLANTIC, TIMI 3 flow of the infarct-related artery before PCI according to pre-hospital administration of ticagrelor did not markedly differ in patients having received morphine or not (14 vs. 21% in patients with ticagrelor and 15 vs. 20% in those without pre-hospital ticagrelor). The reasons for the discrepancy between the impact of pre-hospital administration of ticagrelor on infarct-related artery patency and ST-resolution observed in ATLANTIC remain speculative. In contrast, de Waha *et al.*[14] found

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Table 4 Thrombolysis in Myocardial Infarction 3 flow before percutaneous coronary intervention and mortality with respect to pre-hospital morphine use in patients with pre-hospital clopidogrel, according to genetic variants of CYP2C19 (clopidogrel metabolism) and ABCB1 (clopidogrel absorption)

	Overall population	No pre-hospital morphine	Pre-hospital morphine	*P*-value (Fisher's exact test)
TIMI 3 flow pre-PCI				
CYP2C19 loss-of-function				
0 variant allele, *n* (%)	31/108 (29)	20/73 (27)	11/35 (31)	0.66
1 variant allele, *n* (%)	8/48 (17)	6/39 (15)	2/9 (22)	0.63
2 variant alleles, *n* (%)	0/4 (0)	0/4 (0)	–	–
P for trend	0.049	0.071	0.594	
ABCB1				
CC, *n* (%)	16/43 (37)	11/30 (37)	5/13 (38.5)	1.00
CT, *n* (%)	20/88 (23)	14/62 (23)	6/26 (23)	1.00
TT, *n* (%)	3/28 (11)	1/23 (4.3)	2/5 (40)	0.07
P for trend	0.010	0.006	0.73	
30-day death				
CYP2C19 loss-of-function				
0 variant allele, *n* (%)	3/108 (3)	3/73 (4)	0/35 (0)	0.55
1 variant allele, *n* (%)	0/48 (0)	0/39 (0)	0/9 (0)	–
2 variant alleles, *n* (%)	1/4 (25)	1/4 (25)	–	–
P for trend	0.565	0.730	–	
ABCB1				
CC, *n* (%)	1/43 (2)	1/30 (3.8)	0/13 (0)	1.00
CT, *n* (%)	2/88 (2)	2/62 (3.2)	0/26 (0)	1.00
TT, *n* (%)	1/28 (4)	1/23 (4.3)	0/5 (0)	1.00
P for trend	0.773	0.855	–	
One-year death				
CYP2C19 loss-of-function				
0 variant allele, *n* (%)	8/108 (7)	6/73 (8)	2/35 (6)	1.00
1 variant allele, *n* (%)	1/48 (2)	1/39 (3)	0/9 (0)	1.00
2 variant alleles, *n* (%)	1/4 (25)	1/4 (25)	–	
P for trend	0.757	0.874	0.468	
ABCB1				
CC, *n* (%)	2/43 (5)	1/30 (3.3)	1/13 (7.7)	0.52
CT, *n* (%)	5/88 (6)	4/62 (6.5)	1/26 (3.8)	1.00
TT, *n* (%)	3/28 (11)	3/23 (13)	0/5 (0)	1.0
P for trend	0.339	0.180	0.458	

that intravenous morphine at the acute stage of STEMI reduced reperfusion success after primary PCI as assessed by magnetic resonance imaging, irrespective of pre-PCI TIMI flow. In the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines) registry, 29.8% of patients with non-ST-elevation ACS received morphine within 24 h of presentation,[15] and patients treated with morphine either alone, or in combination with nitroglycerin, had a higher mortality even after risk adjustment (OR 1.41; 95% CI 1.26–1.57).

These results have generated interrogations on the role of morphine in STEMI patients. Indeed, opioids inhibit gastric emptying, which delays absorption and might decrease peak plasma levels of oral drugs.[16] Recently, Hobl *et al.*[3] showed that, in healthy volunteers, administration of morphine retards the absorption of clopidogrel, consequently leading to low initial concentrations of its active metabolite, and thereby delaying the pharmacodynamics (PDs) response by an average of 2 h. At the acute stage of MI, morphine has also been shown to delay absorption of other cardiovascular medications such as isosorbide mononitrate.[17,18]

Our results, both in the whole cohort and in the population having received thienopyridines in the pre-hospital setting, show that the above-mentioned pharmacokinetic (PK) and PD findings do not appear to translate into relevant early or long-term clinical

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consequences. This lack of correlation between PK/PD data and clinical events has also been observed in other instances such as the proton pump inhibitor and clopidogrel interaction.[19] In the FAST-MI 2005 cohort, including both STEMI and non-ST-elevation myocardial infarction patients, genetic polymorphisms of ABCB1 and CYP2C19 were correlated with occurrence of ischaemic events in patients treated with clopidogrel.[6] In the current analysis restricted to STEMI patients treated with pre-hospital clopidogrel, infarct-related artery patency before primary PCI was correlated with *ABCB1* and *CYP2C19* polymorphisms, but no interaction with morphine administration was found regardless of *CYP2C19* and *ABCB1* genetic polymorphisms.

Although the association between pre-hospital morphine administration and 1-year mortality was not statistically significant, the HR indicating a 31% lower risk of death in the 2010 cohort, and a 21% reduction in the 2005 replication cohort, might correspond to a clinically relevant impact and warrants further studies on the clinical role of morphine in this setting. In fact, a plausible explanation of the absence of deleterious clinical impact of morphine is that its favourable haemodynamic effects at the acute stage of MI, namely, a decrease in heart rate without significant change in systolic blood pressure, consistent with previous data,[20] may have counterbalanced any potential deleterious impact in terms of thienopyridine absorption delay.

Study limitations

Our study provides a detailed description of patients pre-treated with morphine in the pre-hospital setting, rarely available from real-world data. It suffers the same limitations as all observational studies, however. Comparisons between patients pre-treated with morphine and those not pre-treated were not randomized and, despite careful adjustments on a large number of potentially confounding variables, the results can only be considered indicative, even if the use of propensity score matching may limit some of the biases inherent to observational data, by giving the opportunity to compare outcomes in cohorts of patients with very similar baseline characteristics. Of note, however, the results in the replication cohort were remarkably consistent with the main analysis. The precise timing of morphine and thienopyridine administration in the ambulance was not available. Finally, because of the relatively small number of patients who had received thienopyridines in the pre-hospital setting and had a genetic evaluation, the results of the analyses according to the genetic profile of CYP2C19 and ABCB1 can only be considered exploratory.

Conclusions

In a routine practice setting, pre-hospital morphine use in STEMI patients was not associated with increased rates of in-hospital complications, including stent thrombosis and 1-year death. At this stage, considerations on the PK/PD interaction between morphine and P2Y12 inhibitors do not seem sufficient to reconsider international guidelines on morphine use in STEMI patients. Pending a specific trial on the use of morphine at the acute stage of myocardial infarction, it still seems advisable to continue using morphine as appropriate in patients with severe chest pain.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Authors' contributions

E.P. and N.D.: performed statistical analysis. T.S. and N.D.: handled funding and supervision, and acquired the data. E.P., T.S., and N.D.: conceived and designed the research, and drafted the manuscript. L.L., N.B., N.A., P.H., G.C., S.C., G.S., L.M., G.D., P.G., F.S., and E.B.-C.: made critical revision of the manuscript for key intellectual content.

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Morphine delays and attenuates ticagrelor exposure and action in patients with myocardial infarction: the randomized, double-blind, placebo-controlled IMPRESSION trial

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Aims The currently available data indicate a drug–drug interaction between morphine and oral P2Y12 receptor inhibitors, when administered together. The aim of this trial was to assess the influence of infused morphine on pharmacokinetics and pharmacodynamics of ticagrelor and its active metabolite (AR-C124910XX) in patients with acute myocardial infarction.

Methods and results In a single-centre, randomized, double-blind trial, patients were assigned in a 1:1 ratio to receive intravenously either morphine (5 mg) or placebo, followed by a 180 mg loading dose of ticagrelor. Pharmacokinetics was determined with liquid chromatography tandem mass spectrometry and ticagrelor antiplatelet effects were measured with up to three different platelet function tests: vasodilator-stimulated phosphoprotein phosphorylation assay, multiple electrode aggregometry and VerifyNow. The pharmacokinetic and pharmacodynamic assessment was performed in 70 patients (35 in each study group). Morphine lowered the total exposure to ticagrelor and its active metabolite by 36% ($AUC_{(0-12)}$: 6307 vs. 9791 ng h/mL; $P = 0.003$), and 37% ($AUC_{(0-12)}$: 1503 vs. 2388 ng h/mL; $P = 0.008$), respectively, with a concomitant delay in maximal plasma concentration of ticagrelor (4 vs. 2 h; $P = 0.004$). Multiple regression analysis showed that lower $AUC_{(0-12)}$ values for ticagrelor were independently associated with the administration of morphine ($P = 0.004$) and the presence of ST-segment elevation myocardial infarction ($P = 0.014$). All three methods of platelet reactivity assessment showed a stronger antiplatelet effect in the placebo group and a greater prevalence of high platelet reactivity in patients receiving morphine.

Conclusions Morphine delays and attenuates ticagrelor exposure and action in patients with myocardial infarction. ClinicalTrials.gov Identifier: NCT02217878.

Keywords Morphine • Ticagrelor • Pharmacodynamics • Pharmacokinetics • Myocardial infarction

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Introduction

Dual antiplatelet therapy with a P2Y12 receptor inhibitor and aspirin plays a pivotal role in the treatment of patients with acute coronary syndromes.[1,2] According to the current guidelines, ticagrelor and prasugrel are recommended preferentially over clopidogrel in patients with acute coronary syndromes undergoing percutaneous coronary intervention (PCI), with class IB indication.[3,4]

The use of morphine in acute coronary syndromes patients is aimed at alleviation of chest pain, anxiety, and ideally at limitation of sympathetic activation. The guidelines for the management of patients with acute myocardial infarction (AMI) continue to recommend i.v. morphine as the drug of choice for pain relief, with class IC indication.[3,4] The analgesic and sedative action of morphine is expected to reduce heart rate and blood pressure, thereby improving the balance between the demand for and supply of oxygen.[5] However, the correlation between pain relief and the cardioprotective effect of morphine has never been demonstrated in randomized controlled trials.[6] Moreover, the CRUSADE registry revealed higher rates of adverse clinical outcomes in non-ST-segment elevation acute coronary syndromes patients treated with clopidogrel who received i.v. morphine, when compared with those who did not.[7] Interestingly, in the ATLANTIC study early, in-ambulance, administration of ticagrelor in patients with ST-segment elevation myocardial infarction (STEMI) transferred for primary PCI, improved coronary reperfusion only in those who did not receive morphine.[8] These findings are in line with pharmacodynamic observations published by Parodi *et al.*,[9–11] suggesting that the onset of action of prasugrel and ticagrelor may be delayed by co-administration of morphine in STEMI patients. Although the existing data from non-randomized trials advocates the presence of drug–drug interaction when morphine and a P2Y12 inhibitor are administered concomitantly in the acute coronary syndromes setting, the definitive evidence of such interaction may be obtained only in a randomized trial. Furthermore, a combined pharmacokinetic-pharmacodynamic study is indispensable to confirm the alleged interaction between morphine and ticagrelor, and potentially provide some clues regarding its underlying mechanism.

Bearing in mind the fact that any delay and attenuation of the platelet blockade in interventionally treated AMI patients may increase the risk of thrombotic complications, this trial assessed the influence exerted by intravenously administered morphine on the pharmacokinetics and pharmacodynamics of ticagrelor and its active metabolite in this setting.

Methods

Study design

A phase IV, single-centre, randomized, double-blind, placebo-controlled trial conducted in accordance with the principles contained in the Declaration of Helsinki and Good Clinical Practice guidelines aimed to assess the influence of morphine on the pharmacokinetics and pharmacodynamics of ticagrelor in patients with myocardial infarction. The diagnosis of STEMI and non-ST-elevation myocardial infarction (NSTEMI) was made according to the third universal definition of myocardial infarction.[12] The study was approved by The Ethics Committee of Nicolaus Copernicus University in Toruń, Collegium Medicum in Bydgoszcz (study approval reference number KB 111/2014). Each patient provided a written informed consent to participate in the study ($n = 74$). Key inclusion criteria were provision of informed consent for angiography and PCI, diagnosis of STEMI or NSTEMI, and males or non-pregnant females aged between 18 and 80 years. Key exclusion criteria were chest pain described by the patient as unbearable, patient's request for analgesics, prior morphine administration during the current AMI, treatment with any P2Y12 receptor inhibitor within 14 days prior to study enrolment, ongoing treatment with oral anticoagulant or chronic therapy with low molecular weight heparin, active bleeding, Killip class III or IV during screening for eligibility, respiratory failure, history of coagulation disorders. The full list of exclusion criteria was previously published.[13]

Consecutive AMI patients admitted to our site between 6:00 a.m. and 6:00 p.m. were screened for eligibility. Time restrictions were related to the expanded schedule of blood collection. Randomization was conducted using Random Allocation Software version 1.0. Randomization kits, either morphine (5 mg; Polfa Warszawa S.A., Warsaw, Poland) or placebo (0.9% NaCl) were injected by blinded physicians. After admission to the study centre (Cardiology Clinic, Dr A. Jurasz University Hospital, Bydgoszcz, Poland) and confirmation of the initial diagnosis of STEMI or NSTEMI, all patients received orally a 300 mg loading dose (LD) of plain aspirin (Polpharma SA, Starogard Gdański, Poland) and were screened for eligibility for the study. Eligible patients, who provided informed consent, were randomly assigned in a 1:1 ratio to one of two study arms. Patients in the intervention arm received a 180 mg LD of ticagrelor with 250 mL tap water immediately after the i.v. injection of 5 mg of morphine. Patients in the control arm received a 180 mg LD of ticagrelor with 250 mL tap water promptly after the i.v. injection of placebo. Subsequently, within 15 min from the ticagrelor LD, all patients underwent a coronary angiography assessment followed by PCI, if necessary.

Endpoints

The primary endpoint of this trial was the area under the plasma concentration–time curve ($AUC_{(0-12)}$) for ticagrelor during the first 12 h after the administration of the LD. Secondary endpoints included $AUC_{(0-12)}$ for AR-C124910XX, $AUC_{(0-6)}$ for ticagrelor and AR-C124910XX, maximum concentration of ticagrelor and AR-C124910XX for 12 h (C_{max12}), time to C_{max} (t_{max}) for ticagrelor and AR-C124910XX, platelet reactivity index (PRI) assessed by the vasodilator-stimulated phosphoprotein (VASP) phosphorylation assay, area under the aggregation curve (AUC) assessed by multiple electrode aggregometry (MEA), P2Y12 reaction units (PRU) assessed by VerifyNow, percentage of patients with high platelet reactivity (HPR) 2 h after the LD of ticagrelor assessed with VASP, MEA and VerifyNow, and time to reach platelet reactivity below the cut-off value for HPR evaluated with VASP, MEA, and VerifyNow.

Blood collection

Blood samples for pharmacokinetic and pharmacodynamic studies were collected using a venous catheter (18G) inserted into a forearm vein. The first 3–5 mL of blood was discarded to avoid spontaneous platelet activation. Samples were drawn at eight pre-defined time points according to the blood sampling schedule (prior to the LD of ticagrelor and 30 min, 1, 2, 3, 4, 6 and 12 h post LD).[13]

Evaluation of pharmacokinetics

Ticagrelor and AR-C124910XX plasma concentrations were analyzed using liquid chromatography coupled with tandem mass spectrometry. Ticagrelor and AR-C124910XX were extracted using 4°C methanol solution containing [2H7]ticagrelor internal standard (TM-ALS-13-226-P1,

ALSACHIM, France). Calibration curves were prepared using ticagrelor (SVI-ALS-13-146, ALSACHIM, France) and AR-C124910XX (TM-ALS-13-193-P1, ALSACHIM, France) standards. Analysis was performed using the Shimadzu UPLC Nexera X2 system consisting of LC-30AD pumps, SIL-30AC Autosampler, CTO-20AC column oven, FCV-20-AH2 valve unit, and DGU-20A5R degasser coupled with Shimadzu 8030 ESI-QqQ mass spectrometer. Lower limits of quantification were 4.69 ng/mL for both ticagrelor and AR-C124910XX.

Pharmacodynamic assessment

Platelet function testing was performed using up to three independent methods. Platelet reactivity in all study participants was assessed with the VASP assay (Biocytex, Inc., Marseille, France). Multiple electrode aggregometry pharmacodynamic evaluation with the Multiplate analyzer (Roche Diagnostics International Ltd., Rotkreuz, Switzerland) was performed in all patients except for those treated with glycoprotein (GP) IIb/IIIa receptor inhibitors. The VerifyNow P2Y12 assay (Accumetrics, Inc., San Diego, USA) was used to assess platelet reactivity in 48 patients (68.6% of patients included in the primary analysis), which was in line with the previously published study protocol.[13] High platelet reactivity was defined as PRI >50%, AUC >46 units (U) and PRU >208, assessed with VASP, Multiplate, and VerifyNow, respectively.[14,15]

Sample size calculation

Since there was no reference study examining the pharmacokinetics of ticagrelor in patients presenting with STEMI or NSTEMI, we decided to perform an internal pilot study of approximately 30 patients (15 for each arm) to estimate the final sample size. Based on the results obtained from the analysis of the first 33 enrolled patients, and assuming a two-sided alpha value of 0.05, we calculated, using the *t*-test for independent variables, that enrolment of 68 patients would provide an 80% power to demonstrate a significant difference in $AUC_{(0-12)}$ for ticagrelor between the study arms.[13]

Statistical analysis

Statistical calculations were performed using the Statistica 12.5 package (StatSoft, Tulsa, OK, USA). Pharmacokinetic calculations and plots were made using the Matlab R2014 software (Mathworks, Natick, MA, USA). Trapezoidal rule was applied to calculate AUC. Data for $AUC_{(0-12)}$ and C_{max} for ticagrelor and AR-C124910XX were presented as means with standard deviations (SD) or with standard error of the mean, and as medians and inter-quartile ranges for t_{max}, $AUC_{(0-6)}$ for ticagrelor and AR-C124910XX, and pharmacodynamic outcome variables. Both C_{max} and t_{max} were evaluated for the period from 0 to 12 h. Continuous variables were compared between both study arms with Student's *t*-test and Mann–Whitney *U* test, depending on the presence or absence of the normal distribution (as assessed by the Shapiro-Wilk test). Comparisons between categorical variables were performed by the χ^2 test, with Yates's correction if necessary, or by Fisher's exact test. To determine variables independently associated with lower $AUC_{(0-12)}$ values for ticagrelor among those listed in *Table 1*, we performed a single linear regression analysis followed by a multiple linear regression analysis. In all cases, two-sided *P*-values <0.05 were considered significant.

Results

Baseline characteristics and in-hospital events

Between August 2014 and June 2015, 74 AMI patients were enrolled into the study (*Figure 1*). The study participants were randomly assigned to receive either morphine ($n = 37$) or placebo ($n = 37$). The pharmacokinetic and pharmacodynamic assessment was eventually performed in 70 patients (35 in each study group). Baseline characteristics were well balanced between both groups (*Table 1*). In-hospital adverse, ischaemic and bleeding events are reported in *Table 2*. There were no significant differences in the event rates between the study arms. However, numerically higher rates of nausea and vomiting were observed in the morphine group, while minor bleedings were numerically more frequent in the placebo arm.

Table 1 Baseline characteristics of study patients

Variable	Morphine (%) ($n = 35$)	Placebo (%) ($n = 35$)	*P*-value
Age, years	60.7 ± 10.5	62.5 ± 10.5	0.47
Female	12 (34)	7 (20)	0.19
Body mass index, kg/m^2	27.6 ± 4.3	27.4 ± 4.0	0.87
STEMI	24 (69)	21 (60)	0.45
GP IIb/IIIa administration	10 (28)	6 (17)	0.25
Metoclopramide use	1 (3)	0 (0)	n/a
Hypertension	15 (43)	21 (60)	0.15
Diabetes mellitus	8 (23)	5 (14)	0.36
Dyslipidaemia	30 (86)	31 (89)	n/a
Current smoker	17 (55)	14 (45)	0.47
Prior AMI	5 (14)	8 (23)	0.20
Prior PCI	4 (11)	9 (26)	0.12
Prior CABG	0 (0)	0 (0)	n/a
Prior non-severe heart failure	0 (0)	3 (9)	0.08
Prior non-haemorrhagic stroke	1 (3)	0 (0)	0.31
Peripheral arterial disease	3 (9)	1 (3)	0.31
Chronic renal disease	1 (3)	2 (6)	0.31
Chronic obstructive pulmonary disease	2 (6)	0 (0)	n/a
Gout	1 (3)	2 (6)	n/a

Data are shown as mean ± standard deviation or number (%).
AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; GP, glycoprotein; n/a, not applicable; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

Pharmacokinetics

Administration of morphine when compared with placebo resulted in lower total exposure to both ticagrelor and its active metabolite AR-C124910XX within the first 12 h after the administration of the 180 mg ticagrelor LD, as measured by the $AUC_{(0-12)}$ (ticagrelor: 6307 ± 4359 vs. 9791 ± 5136 ng h/mL; corresponding to a difference of 36%; $P = 0.003$, *Figure 2A*; AR-C124910XX: 1503 ± 1138 vs. 2388 ± 1555 ng h/mL; difference: 37%; $P = 0.008$, *Figure 2B*). The observed differences in total exposure were even more pronounced within the first 6 h [$AUC_{(0-6)}$ for ticagrelor: 2491 (189–5764) vs. 5587 (2810–8546) ng h/mL; difference: 55%; $P = 0.002$; $AUC_{(0-6)}$ for AR-C124910XX: 472 (0–1036) vs. 1001

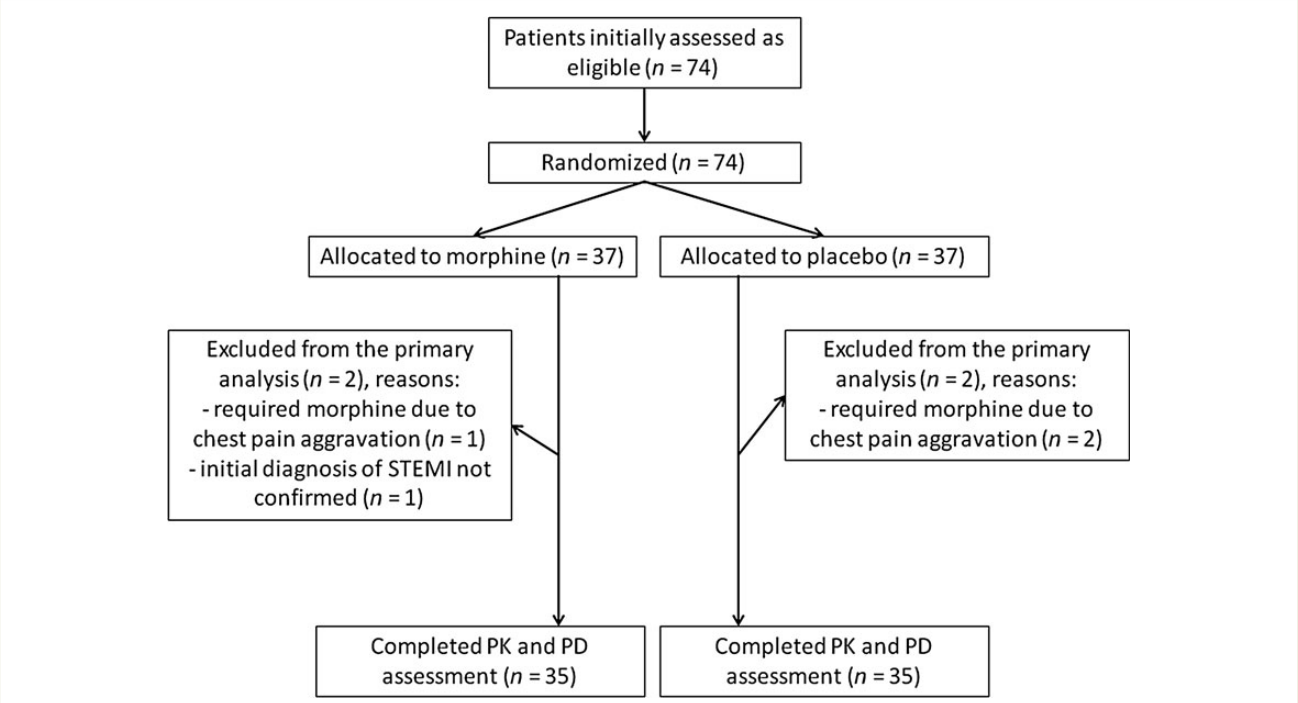

Figure 1 Patient flow diagram. PD, pharmacodynamic; PK, pharmacokinetic; STEMI, ST-elevation myocardial infarction.

Table 2 In-hospital adverse, ischaemic and bleeding events

In-hospital events	Morphine (%) (*n* = 35)	Placebo (%) (*n* = 35)	*P*-value
Death	0 (0)	0 (0)	n/a
Myocardial infarction	0 (0)	0 (0)	n/a
Stent thrombosis	1 (3)	0 (0)	n/a
Pulmonary oedema	0 (0)	2 (6)	n/a
Stroke	0 (0)	0 (0)	n/a
TIMI major bleeding	0 (0)	0 (0)	n/a
TIMI minor bleeding	0 (0)	4 (11)	n/a
TIMI minimal bleeding	0 (0)	1 (3)	n/a
Dyspnoea	0 (0)	0 (0)	n/a
Bradyarrhythmic event	1 (3)	2 (6)	n/a
Nausea	2 (6)	0 (0)	n/a
Vomiting	2 (6)	0 (0)	n/a

Data are shown as number (%).
n/a, not applicable; TIMI, thrombolysis in myocardial infarction.

(643–1666) ng h/mL; difference: 53%; $P = 0.006$]. Maximal plasma concentrations of ticagrelor in patients receiving morphine were delayed when compared with placebo [t_{max} for ticagrelor: 4 (3–12) vs. 2 (2–4) h; $P = 0.004$] and reduced (C_{max} for ticagrelor: 1156 ± 771 vs. 1683 ± 847 ng/mL; $P = 0.006$). Simple regression analysis showed that lower $AUC_{(0-12)}$ values for ticagrelor were associated with the administration of morphine ($P = 0.003$) and the presence of STEMI ($P = 0.010$), but not with other variables displayed in *Table 1*. Additionally, multiple regression analysis confirmed both morphine administration (beta-coefficient = −0.32; $P = 0.004$) and the presence of STEMI (beta-coefficient = −0.28; $P = 0.014$) to be independent predictors of low $AUC_{(0-12)}$ values. The R^2 value of 0.17 indicated that 17% of the variability in $AUC_{(0-12)}$ for ticagrelor can be explained by this model. Of note, the $AUC_{(0-12)}$ for ticagrelor was on average 2901 ± 1148 ng h/mL lower in the STEMI vs. NSTEMI group ($P = 0.014$). After adjustment for AMI type (STEMI vs. NSTEMI), a mean decrease in $AUC_{(0-12)}$ of 3236 ± 1101 ng h/mL was found in morphine-treated patients when compared with the placebo group ($P = 0.004$).

Pharmacodynamics

Assessment of platelet reactivity with three different methods provided consistent results showing a stronger antiplatelet effect in the placebo group than in morphine-treated patients. According to MEA, co-administration of morphine resulted in a significantly higher platelet reactivity at all measurement points except for the baseline (*Figure 3A*). Consistent, however slightly less pronounced, results were obtained for the VASP and VerifyNow P2Y12 tests (*Figure 3B* and *C*). The number of patients with HPR was higher in the morphine group (*Figure 4*), reflecting an impaired antiplatelet effect of ticagrelor in patients receiving morphine when compared with the placebo group. The prevalence of HPR was numerically higher for the morphine vs. placebo arm at all measurement points, irrespectively of the method of platelet function assessment to be applied. However, the differences between the compared groups reached statistical significance for 30 min, 1 and 2 h (pre-specified

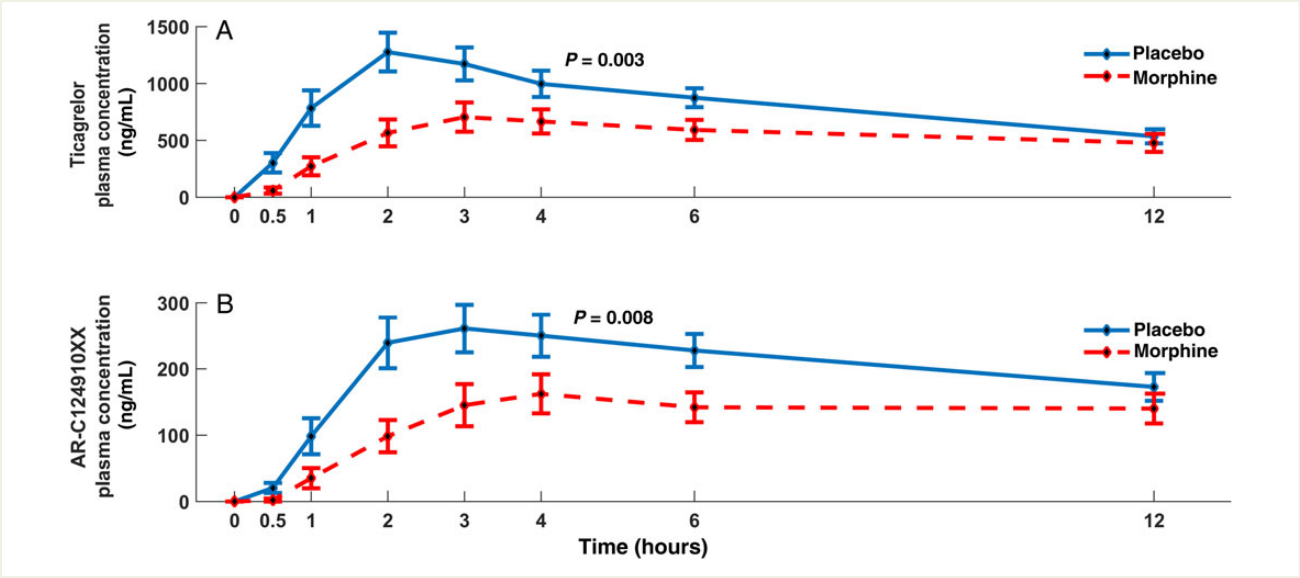

Figure 2 Plasma concentrations of ticagrelor and AR-C124910XX. Plasma concentrations of (*A*) ticagrelor and (*B*) AR-C124910XX after oral administration of a 180 mg ticagrelor loading dose, which followed intravenous injection of placebo (blue) or morphine (red).

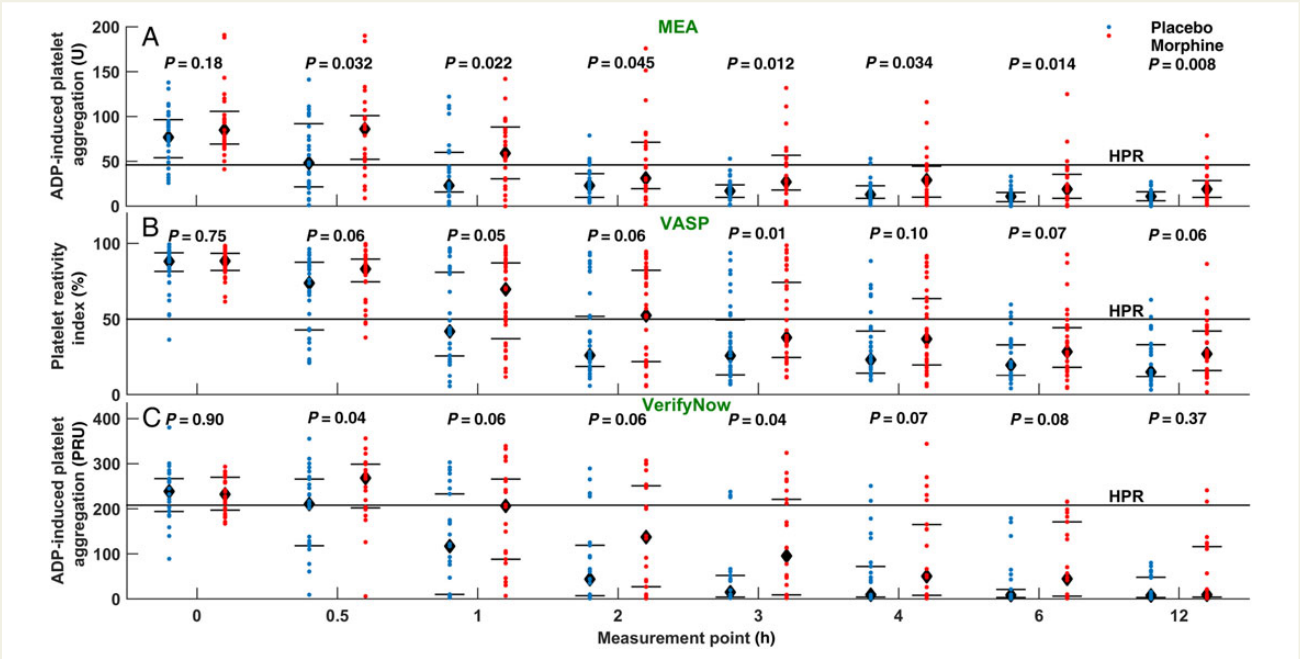

Figure 3 Platelet reactivity over time in morphine vs. placebo-treated patients. Platelet reactivity assessed with (*A*) MEA ($n = 54$), (*B*) VASP ($n = 70$), and (*C*) VerifyNow P2Y12 ($n = 48$) tests at baseline, and at 30 min, 1, 2, 3, 4, 6, and 12 h after administration of a 180 mg ticagrelor loading dose in morphine (red) vs. placebo (blue)-treated patients. ADP, adenosine diphosphate; HPR, high platelet reactivity; MEA, multiple electrode aggregometry; PRU, P2Y12 reaction units; VASP, vasodilator-stimulated phosphoprotein; U, units.

secondary endpoint), 3 h measurement points and for 1 and 2 h (pre-specified secondary endpoint) measurement points for MEA and for the VASP assay, respectively. Additionally, morphine increased the lag time to reach platelet reactivity below the cut-off values for HPR when compared with placebo patients [MEA: 2.0 (1.0–4.0) vs. 1.0 (0.5–2.0) h; $P = 0.007$; VASP: 2.0 (1.0–6.0) vs. 1.0 (0.5–3.0) h; $P = 0.03$; VerifyNow P2Y12: 1.0 (0.0–3.0) vs. 0.5 (0.0–1.0) h; $P = 0.33$].

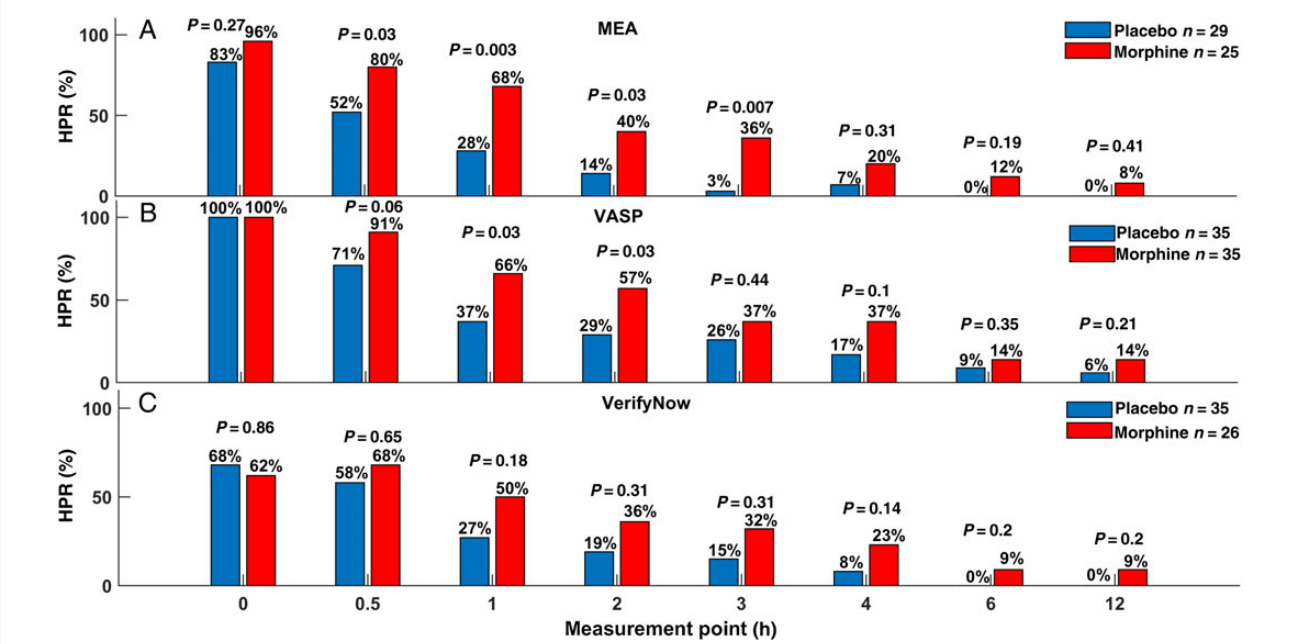

Figure 4 Prevalence of high platelet reactivity over time in morphine vs. placebo-treated patients. Proportion of patients with high platelet reactivity assessed with (*A*) MEA, (*B*) VASP, and (*C*) VerifyNow P2Y12 tests at pre-defined measurement points in relation to administration of morphine (red) or placebo (blue). HPR, high platelet reactivity; MEA, multiple electrode aggregometry; VASP, vasodilator-stimulated phosphoprotein.

Discussion

To our knowledge, the current trial is the first one to confirm the negative impact exerted by morphine on the pharmacokinetics and antiplatelet action of ticagrelor in AMI patients obtained in a randomized study. Co-administration of morphine led to reduced exposure to ticagrelor and its active metabolite. It also delayed and attenuated maximal plasma concentrations of ticagrelor. Additionally, the unfavourable influence of morphine on the pharmacokinetics of ticagrelor resulted in a weaker and retarded antiplatelet effect of ticagrelor.

The CRUSADE registry showed that use of morphine, either alone or in combination with nitroglycerin, in patients presenting with non-ST-segment elevation acute coronary syndromes and treated with clopidogrel was associated with higher mortality. This detrimental effect persisted even after risk adjustment and matching on propensity score for treatment.[7] Moreover, in the ATLANTIC study upstream administration of ticagrelor when compared with its downstream use facilitated ST-segment resolution only in STEMI patients transferred for primary PCI, who did not receive morphine.[8]

Although we did not investigate the underlying mechanism of our findings in detail, it seems likely that morphine impairs absorption of ticagrelor. Morphine was demonstrated to activate the opioid receptors located in the myenteric plexus and in the intestines and to decrease propulsive motility and secretion of the gastro-intestinal tract.[16] In our study, decreased total exposure to ticagrelor within 6 ($AUC_{(0-6)}$) and 12 ($AUC_{(0-12)}$) h after the administration of a 180 mg ticagrelor LD by 55 and 36%, respectively, was reflected by a similar reduction of total exposure to AR-C124910XX. Lower overall concentrations and delayed maximal concentrations of ticagrelor (on average by 2 h) resulted in impaired and retarded pharmacodynamic responses. Similar observations regarding the influence of morphine on the pharmacokinetics and pharmacodynamics of clopidogrel in healthy volunteers were recently published by Hobl *et al.*[17] On-ticagrelor platelet reactivity was higher in our study in morphine-treated AMI patients when compared with those receiving placebo within first 6 h since drug administration. Similarly, the prevalence of HPR, indicating increased risk of ischaemic outcomes,[18] was lower in the placebo vs. morphine group in the majority of the measurement points, with the most pronounced difference between 0.5 and 4 h after administration of a 180 mg ticagrelor LD. Hence, we consider the observed reduction in the antiplatelet effect of ticagrelor to be clinically relevant. Our findings correspond with the results of the observational pharmacodynamic studies published by Parodi *et al.*[9–11] Data from two single-centre studies and one multi-centre patient-level integrated analysis exploring the effect of morphine on platelet reactivity in STEMI patients treated with ticagrelor or prasugrel provided consistent information, suggesting existence of a drug–drug interaction.[9–11] According to these solely pharmacodynamic observations, the independent predictors of HPR at 2 h were: morphine use [odds ratio (OR) 2.91; $P < 0.0001$] and age (OR 1.03; $P = 0.01$). Morphine administration remained significantly associated with HPR (OR 1.89; $P < 0.001$) after propensity score adjustment.[11]

The ticagrelor–morphine interaction that was revealed in the IMPRESSION study warrants prompt investigation in clinically powered randomized trials in the AMI setting. Although morphine administration may potentially lead to detrimental clinical consequences in AMI patients, its routine avoidance cannot be recommended until such trials are completed. Importantly, pain relief

remains one of the major therapeutic aims in the management of AMI. Additionally, the optimal intensity of antiplatelet therapy in AMI patients undergoing PCI is a matter of ongoing debate. Some possible strategies overcoming or at least diminishing the negative impact of morphine on the antiplatelet effect of oral P2Y12 receptor inhibitors in AMI patients include: use of cangrelor, a novel i.v. P2Y12 receptor inhibitor, or concomitant administration of a GP IIb/IIIa receptor inhibitor, use of a prokinetic agent – metoclopramide, administration of crushed ticagrelor tablets and replacement of morphine by a short-acting analgesic, alfentanil.[19,20] However, such management should be evaluated in further studies.

Study limitations

Several limitations of our study need to be acknowledged. First, the study sample size was insufficient to assess the effect of morphine on clinical endpoints and to perform subgroup analyses. Second, even though the study arms were well balanced and multivariate analysis indicated morphine administration as an independent predictor of low ticagrelor exposure, it has to be admitted that inclusion of both STEMI and NSTEMI patients introduced heterogeneity into the study population. Third, the observed drug–drug interaction might be enhanced by the administration of higher morphine doses or by longer time intervals from morphine administration to the ticagrelor LD, which were not tested in the current study. Fourth, although the results of the pharmacodynamic analysis consistently showed delayed and attenuated antiplatelet effect of ticagrelor in morphine-treated patients, the differences between the study arms in some measurement points did not reach statistical significance. Finally, the detailed underlying mechanism of our findings warrants further investigation.

Conclusions

Morphine delays and attenuates ticagrelor exposure and action in patients with myocardial infarction.

Authors' contributions

J.K., P.A., M.O., J.S., J.M.K., W.D.S., K.S., K.B., E.P.N., B.J., J.M.S.-M., M.P.M., D.R., M.K.: performed statistical analysis.

J.K., P.A., M.O., J.S., J.M.K., W.D.S., K.S., K.B., E.P.N., B.J., J.M.S.-M., M.P.M., D.R., M.K.: handled funding and supervision.

J.K., P.A., M.O., J.S., J.M.K., W.D.S., K.S., K.B., E.P.N., B.J., J.M.S.-M., M.P.M., D.R., M.K.: acquired the data.

J.K., P.A., M.O., M.K.: conceived and designed the research

J.K., P.A., M.O., J.S., J.M.K., W.D.S., K.S., K.B., E.P.N., B.J., J.M.S.-M., M.P.M., D.R., M.K.: drafted the manuscript.

J.K., P.A., M.O., J.S., J.M.K., W.D.S., K.S., K.B., E.P.N., B.J., J.M.S.-M., M.P.M., D.R., M.K.: made critical revision of the manuscript for key intellectual content.

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CARDIOVASCULAR FLASHLIGHT

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Pseudoaneurysm following transradial coronary angiogram

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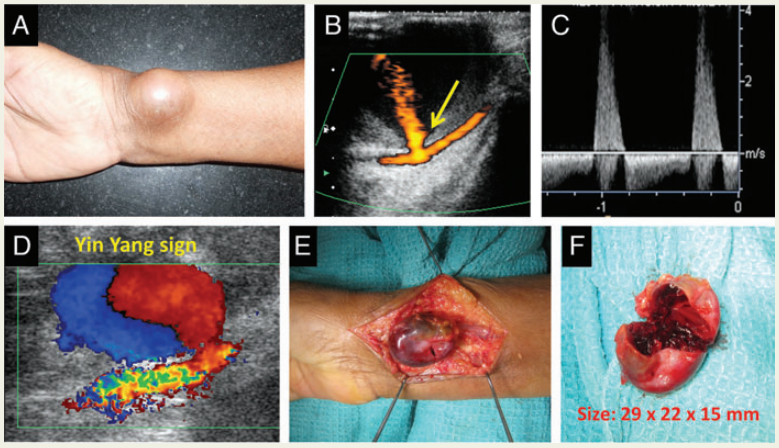

A 54-year-old lady presented with Canadian cardiovascular society class II stable angina of 6 months duration. Clinical examination and investigations were unremarkable, including normal echocardiogram. She underwent elective coronary angiogram through right radial access, which revealed double vessel disease, and was discharged 6 h after the procedure. Two months afterwards, she presented with progressively enlarging swelling at the radial puncture site. Physical examination showed non-tender pulsatile hemispherical swelling on the volar aspect of right wrist (*Panel A*). Duplex ultrasound examination confirmed the presence of radial artery pseudoaneurysm measuring 29 × 22 × 15 mm, with a narrow neck of 2.7 mm (*Panel B*, arrow points to the neck of aneurysm). Spectral Doppler showed high velocity to and fro flow across the aneurysm neck (*Panel C*) and the classical yin-yang sign the characteristic swirling motion of blood in the aneurysm (*Panel D*). There was absence of distal flow in the radial artery, although the integrity of flow in the ulnar artery and palmar arch was preserved. In view of the large size of the aneurysm and its chronicity, patient was referred for surgical repair. Excision of the pseudoaneurysm and ligation of the radial artery was performed successfully (*Panels E* and *F*). She recovered well and subsequently underwent coronary angioplasty through the right femoral access. Patient is asymptomatic at 6 months follow-up with no recurrence of swelling. Access-related complications, although rare following radial procedures, is well recognized; meticulous care of arterial puncture site goes a long way in preventing this avoidable complication.

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ORIGINAL INVESTIGATION

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In-hospital outcomes in invasively managed acute myocardial infarction patients who receive morphine

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Objective: We aimed to analyze the association between morphine and in-hospital outcomes in invasively managed ST elevation myocardial infarction (STEMI) and non-ST elevation acute coronary syndrome (NSTE-ACS) patients.

Background: Morphine is commonly used for analgesia in the setting of acute coronary syndromes (ACS); however, recently its utility in ACS has come under closer scrutiny.

Methods: We identified all STEMI and NSTE-ACS patients undergoing coronary angiogram +/− percutaneous intervention between January 2009 and July 2016 in our center and recorded patient characteristics and inpatient outcomes.

Results: Overall, 3027 patients were examined. Overall, STEMI patients who received morphine had no difference in in-hospital mortality [4.18% vs. 7.54%, odds ratio (OR): 0.36, $P = 0.19$], infarct size (mean troponin level 0.75 ng/mL vs. 1.29 ng/mL, $P = 0.32$) or length of hospital stay ($P = 0.61$). The NSTE-ACS patients who received morphine had a longer hospital stay (mean 6.58 days vs. 4.78 days, $P < 0.0001$) and larger infarct size (mean troponin 1.16 ng/mL vs. 0.90 ng/mL, $P = 0.02$). Comparing matched patients, the use of morphine was associated with larger infarct size (mean troponin 1.14 ± 1.92 ng/mL vs. 0.83 ± 1.49 ng/mL, $P = 0.01$), longer hospital stay (6.5 ± 6.82 days vs. 4.89 ± 5.36 days, $P = 0.004$) and a trend towards increased mortality (5% vs. 2%, OR: 2.55, $P = 0.06$) in NSTE-ACS patients but morphine did not affect outcomes in the propensity matched STEMI patients.

Conclusion: In a large retrospective study, morphine was associated with larger infarct size, a longer hospital stay and a trend towards increased mortality in invasively managed NSTE-ACS patients even after adjustment for clinical characteristics.

KEYWORDS
morphine, NTE-ACS, STEMI

1 | INTRODUCTION

Since the early 1900's morphine has become a commonly used analgesic in acute coronary syndromes (ACS).[1,2] Potent analgesic properties, limited alternative agents, and perceived reduction in

Abbreviations: ACS, acute coronary syndrome; CI, confidence interval; EKG, electrocardiogram; MI, myocardial infarction; NSTE, ACS- non-ST elevation acute coronary syndrome; OR, odds ratio; PCI, percutaneous coronary intervention; SD, standard deviation; STEMI, ST segment elevation myocardial infarction.

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myocardial demand, have resulted in longstanding support by both the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) and the European Society of Cardiology (ECS) for the treatment of nitrate resistant chest pain due to acute myocardial infarction (MI).[3–6]

Despite the utilization of this agent in up to 30% of ACS patients,[7] there is limited evidence supporting the use of morphine in this cohort. Furthermore, in 2005, a concerning retrospective observational analysis of 57 039 patients from the CRUSADE registry found that morphine recipients with non-ST elevation acute coronary syndromes (NSTE-ACS) had a significantly higher likelihood of recurrent MI [odds ratio (OR), 1.34], death (OR, 1.48), and the composite endpoint of death or recurrent MI (OR, 1.44) during the initial admission.[7] However, only 36.5% of the patients included in this registry received percutaneous coronary intervention (PCI). As such, it is possible that the association between morphine and increased mortality in this study may be due to its administration in palliative or pre-terminal care. Furthermore, since then, smaller observational studies in both ST elevation myocardial infarction (STEMI) and NSTE-ACS cohorts have also challenged this association of worse outcomes.[8–10] Yet, recent emerging evidence, including a small randomized controlled trial, suggests that morphine may inhibit and delay the absorption of oral anti-platelet agents with resultant delay in time to maximal platelet inhibition.[11–14] Given the importance of rapid platelet inhibition in ACS, this may have significant implication on clinical outcomes.

In light of these concerns, we have undertaken a large single center retrospective analysis of both STEMI and NSTE-ACS patients undergoing coronary angiogram +/− PCI comparing inpatient outcomes in patients who received morphine and those who did not specifically in patients managed invasively.

2 | METHODS

2.1 | Study population

All STEMI and NSTE-ACS patients undergoing coronary angiogram +/− percutaneous intervention between 2009 and 2016 in Massachusetts General Hospital were included in our study. STEMI was defined as a new ST elevation at the J point in two contiguous leads of >0.1 mV in all leads other than leads V2–V3. For leads V2–V3 the following cut points were used: ≥0.2 mV in men ≥40 years, ≥0.25 mV in men <40 years, and ≥0.15 mV in women. A new left bundle branch block and an isolated posterior MI were also considered as STEMIs. NSTE-ACS patients comprised those with ST depressions or T wave inversions on EKG. The 99th percentile cutoff point for cardiac troponin T was 0.01 ng/mL (with 10% coefficient of variance value at the 99th percentile of 0.03 ng/mL). Data was collected during the initial hospitalization in an anonymous fashion and stored in the Massachusetts General Hospital cardiac catheterization database. Following institutional board review approval, baseline patient characteristics (demographics, risk factors, and medical history) was obtained. Data collected included medical therapy administered, admission date/time, procedure date/time, door to balloon time, post procedure TIMI flow, coronary thrombus frequency, technical success (defined as residual stenosis of ≤20% and TIMI 3 flow in all treated vessels), procedural success (defined as technical success and no major adverse cardiovascular event during hospital stay), early stent thrombosis (<30 days of procedure), late stent thrombosis (≥30 days post procedure), inpatient mortality, length of hospital stay, peak troponin level, post-procedure cardiogenic shock, and post-procedure renal failure. The door time was defined as the arrival date and time to the ED or the catheterization lab. If ST elevation was not present on admission but did appear on a subsequent EKG, the date and time of that subsequent EKG was considered the door time. The balloon time was defined as the date and time the first device was activated, be it a balloon, stent, or thrombectomy device. In the rare case that the lesion could not be crossed, the time of guidewire introduction was used.

2.2 | Clinical outcomes

Clinical outcomes recorded included inpatient mortality, post procedure cardiogenic shock, post procedure acute renal failure, length of hospital stay, and infarct size as measured by peak troponin level.

2.3 | Statistical analysis

Patient characteristics and in-hospital clinical outcomes were compared across two groups, patients who received morphine and patients who did not receive morphine. Means +/− standard deviations were reported for continuous variables and frequencies with percentages for categorical variables. Student's *t*-tests were used to check for differences for continuous variables and chi-square tests were used for categorical variables.

There were two sets of multivariate analyses, one without propensity score matching and one with propensity score 1:1 matching. For the first set of analyses, we compared patients who received morphine to those who did not receive morphine with respect to outcomes. Logistic regression was used for binary outcomes (in-hospital mortality, post-procedural cardiogenic shock, and post-procedural renal failure). Linear regression was used for continuous outcomes (length of hospital stay and infarct size, as measured by peak troponin level) Each outcome was reported as 1) unadjusted, 2) adjusted for age and sex, and 3) adjusted for age, sex, body mass index, family history of coronary artery disease, shock at the start of percutaneous coronary intervention, hypertension, diabetes, smoking status, hypercholesterolemia, heart rate, systolic blood pressure, door to balloon time, prior coronary artery bypass grafting, congestive heart failure, cerebrovascular disease, and renal insufficiency.

As an additional method of accounting for nonrandom morphine treatment assignment, we adjusted for factors favoring selection of one treatment over another by using propensity scores. Using logistic regression, a propensity score model was created to estimate the likelihood of morphine treatment, separately for the STEMI (107 patients in each group) and NSTEMI (306 patients in each group) population. The differences between the two matched cohorts for both STEMI and NSTEMI samples were assessed by calculating the

absolute value of the standardized differences, and was always <10%, except for previous coronary intervention in the STEMI population (−13.34) and congestive heart failure in the NSTEMI population (13.44). The propensity score analysis was then used to apply the same regression analyses as prior and reported as 1) unadjusted, 2) adjusted for age and sex, and 3) age, sex, and other clinical covariates. For all analyses, a two-sided *P*-value of <0.05 was established as the level of statistically significance. All analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC). This analysis was approved by the Institutional Review Board at Partners Healthcare.

3 | RESULTS

3.1 | Baseline characteristics

During the study period, there were 10 126 patients admitted with acute MI to our center. There were 5990 STEMI cases and 4136 NSTE-ACS cases. 3027 patients who underwent PCI were examined in our study. There were 1287/3027 (42.52%) STEMI cases, of which 359/1287 patients received morphine (27.89%). STEMI patients who received morphine were younger, had a higher prevalence of previous MI, PCI, and angina, were more likely to be on oxygen therapy, and had a longer door to balloon time (Table 1). There were 1740/3027 (57.48%) NSTE-ACS cases, of which 424 (24.37%) received morphine. NSTE-ACS patients who received morphine were younger, had a higher prevalence of cerebrovascular disease, peripheral vascular disease, prior PCI, MI, congestive heart failure, and valvular surgery (Table 2).

3.2 | Morphine versus no morphine: in-hospital outcomes

In unadjusted outcomes, STEMI patients who received morphine had a lower in-hospital mortality (4.18% vs. 7.54%, OR 0.53 $P = 0.03$) and smaller infarct size (mean troponin level 0.75 ng/mL vs. 1.29 ng/mL, $P = 0.02$) (Table 3). There was no significant difference in post-procedure cardiogenic shock [1.95% in morphine cohort vs. 3.13% in non-morphine cohort, OR 0.62, $P = 0.26$], post-procedural renal failure (1.95% in morphine cohort vs. 3.77% in the non-morphine cohort, OR 0.50, $P = 0.11$), or length of hospital stay (mean 5.40 days in the morphine cohort vs. 5.91 in the non-morphine cohort, $P = 0.29$). After adjusting for basic characteristics the reduction in mortality and infarct size was not significant ($P = 0.19$ and $P = 0.32$, respectively). STEMI patients who received morphine had a trend towards an increased frequency of coronary thrombus (54% in morphine recipients vs. 48% in non-morphine recipients, $P = 0.07$). There was no difference in the incidence of early stent thrombosis (2.2% in morphine group vs. 1.6% in non-morphine recipients, $P = 0.47$) or of late stent thrombosis between each group (1.1% in morphine group vs. 1.2% in non-morphine recipients, $P = 0.91$).

In the NSTE-ACS cohort, patients who received morphine had higher post-procedure acute renal failure (4.25% vs. 2.13%, OR 2.04, $P = 0.02$), longer length of hospital stay (mean 6.58 days vs. 4.78, $P < 0.0001$) and larger infarct size (mean peak troponin 1.16 ng/mL vs. 0.90 ng/mL, $P = 0.05$) (Table 4). There was no statistical difference in in-hospital mortality between the morphine and non-morphine NSTE-ACS cohorts (3.77% vs. 2.51%, respectively, OR 1.53, $P = 0.17$) or cardiogenic shock (0.71% vs. 0.84% respectively, OR 0.85, $P = 0.80$). After adjusting for basic characteristics, length of hospital stay ($P < 0.0001$) and infarct size ($P = 0.02$) remained significant (Table 4). NSTE-ACS patients who received morphine had an increased frequency of coronary thrombus (13% in morphine recipients vs. 8% in non-morphine recipients, $P = 0.002$). There was no difference in the incidence of early stent thrombosis (0.7% in morphine group vs. 0.8% in non-morphine recipients, $P = 0.79$) or of late stent thrombosis between each group (0.9% in morphine group vs. 1.2% in non-morphine recipients, $P = 0.64$).

3.3 | Propensity score matched cohorts

Two propensity score-matched cohorts of 107 patients with similar baseline characteristics were built from the STEMI cohort (see supplementary material for list of variables, Table S1). In adjusted outcomes, inpatient mortality was similar between those STEMI patients who received morphine and those who did not (8% vs. 11%, respectively, OR: 0.73, $P = 0.34$). There was no difference in length of hospital stay (6.98 ± 10.17 days vs. 7.71 ± 13.11 days, $P = 0.81$) or infarct size as measured by troponin level (1.11 ± 2.65 vs. 1.84 ± 4.68, $P = 0.67$) between the morphine and non-morphine recipients, respectively (Table 5).

In the NSTE-ACS cohort, two propensity score-matched cohorts of 306 patients with similar baseline characteristics was created. In adjusted outcomes (Table 6), NSTE-ACS patients who received morphine had a trend towards increased mortality (5% vs. 2%, OR: 2.36, $P = 0.06$). Notably, morphine recipients had larger infarct size as measured by troponin (1.14 ± 1.92 ng/mL vs. 0.83 ± 1.49 ng/mL, $P = 0.01$) and longer hospital stay (6.5 ± 6.82 days vs. 4.89 ± 5.36 days, $P = 0.004$).

4 | DISCUSSION

In our large single center retrospective study, NSTE-ACS patients who were recipients of morphine had 1) larger infarct size, 2) prolonged hospital stay, and 3) a trend towards increased mortality. In contrast, in STEMI patients who were recipients of morphine, there was no such signal of adverse outcomes.

Given our focus on patients invasively managed with PCI, our study is consistent with and adds to the growing body of evidence to suggest morphine may be associated with harm in NSTE-ACS patients.[7] The largest retrospective study in NSTE-ACS patients which included 57 039 patients from the CRUSADE registry, found that patients treated with morphine had a higher adjusted risk of death (odds ratio [OR] 1.48, 95%CI 1.33-1.64), with such findings persisting after propensity score matching (OR 1.41, 95%CI 1.26-1.57).[7] Given that most patients in CRUSADE did not receive PCI (63.55 of patients),

TABLE 1 Baseline characteristics of STEMI patients who received morphine compared to those who did not

Characteristics	STEMI patients who did not receive morphine (*N* = 928)	STEMI patients who received morphine (*N* = 359)	*P*-value
Demographics			
Age (years) ± SD	62 ± 13	60 ± 12	0.03
Female sex, *n* (%)	250 (27)	80 (22)	0.09
BMI (kg/m^2) ± SD	28.4 ± 5.3	28.9 ± 5.5	0.07
Smoker, *n* (%)	272 (29)	120 (33)	0.12
Medical history			
Cerebrovascular disease, *n* (%)	63 (7)	29 (8)	0.42
Peripheral vascular disease, *n* (%)	78 (8)	28 (8)	0.72
Chronic lung disease, *n* (%)	66 (7)	32 (9)	0.27
Congestive heart failure, *n* (%)	48 (5)	17 (5)	0.75
Family history of CAD, *n* (%)	192 (21)	92 (26)	0.06
Hypercholesterolemia, *n* (%)	840 (91)	340 (95)	0.02
Hypertension, *n* (%)	558 (60)	203 (57)	0.24
Previous CABG, *n* (%)	39 (4)	19 (5)	0.40
Previous PCI, *n* (%)	143 (15)	78 (22)	0.007
Previous MI, *n* (%)	137 (15)	77 (21)	0.004
Diabetes history, *n* (%)	206 (22)	76 (21)	0.69
Creatinine level, (mg/dL) ± SD	1.13 ± 0.72	1.07 ± 0.38	0.04
Prior renal failure, *n* (%)	22 (2)	5 (1)	0.27
Cardiac transplant, *n* (%)	1 (0.1)	0 (0)	1.00
Prior valvular surgery, n (%)	8 (1)	4 (1)	0.75
Utility of anti-anginal agents (2 weeks prior), *n* (%)	314 (34)	119 (33)	0.91
Pre-procedure characteristics			
Heart rate, (beat/min) ± SD	82 ± 19	81 ± 18	0.32
Systolic BP (mmHg) ± SD	124 ± 23	125 ± 21	0.54
Diastolic BP (mmHg) ± SD	79 ± 15	81 ± 14	0.22
Oxygen saturation (%) ± SD	95 ± 5	95 ± 5	0.32
Supplemental oxygen given, *n* (%)	753 (81)	312 (87)	0.01
Thrombolysis pre-procedure, *n* (%)	11 (1)	5 (1)	0.78
Shock at start of PCI, *n* (%)	115 (12)	24 (7)	0.004
Cardiac arrest (prior 24 h), *n* (%)	107 (12)	26 (7)	0.03
Door to balloon time, (min) ± SD	56 ± 56	68 ± 49	0.0005
Pre-procedural medications			
Beta blockers, *n* (%)	278 (30)	104 (29)`	0.74
Calcium channel blockers, *n* (%)	94 (10)	35 (10)	0.92
Nitrates, *n* (%)	30 (3)	13 (4)	0.67
Ranolazine, *n* (%)	-	2 (0.5)	0.02
Aspirin, *n* (%)	859 (93)	322 (90)	0.11
Clopidogrel, *n* (%)	645 (70)	264 (74)	0.15
Ticagrelor, *n* (%)	216 (23)	74 (21)	0.31
Ticlopidine, *n* (%)	-	-	-
Unfractionated heparin, *n* (%)	776 (84)	305 (85)	0.56
Fractionated heparin, *n* (%)	2 (0.2)	-	0.38

(Continues)

TABLE 1 (Continued)

Characteristics	STEMI patients who did not receive morphine (*N* = 928)	STEMI patients who received morphine (*N* = 359)	*P*-value
Bivalirudin, *n* (%)	187 (20)	64 (18)	0.35
Culprit lesions			
Left main coronary artery	13	2	0.21
Left anterior descending artery	327	140	0.20
Circumflex artery	93	29	0.29
Diagonal arteries	22	5	0.27
Marginal arteries	50	18	0.79
Right coronary artery	373	143	0.92
Posterior descending artery	19	9	0.61
Ramus intermedius artery	7	1	0.33
Procedural characteristics			
Technical success rates *n* (%)	825 (89)	313 (87)	0.26
Procedural success rates *n* (%)	754 (81)	300 (84)	0.52
Coronary thrombus, *n* (%)	445 (48)	194 (54)	0.07
Post-procedural TIMI 3 flow, *n* (%)	899 (97)	350 (97)	0.96

BP, blood pressure; BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; MI, myocardial infarction; N, patient number; PCI, percutaneous coronary intervention; SD, standard deviation; STEMI, ST segment elevation myocardial infarction.

these results may have been influenced by an association between high-risk patients being turned down for PCI receiving more morphine. In that context, the fact that we have found similar findings in a population all of whom were referred for coronary angiography strengthens the evidence that morphine may be harmful for NSTE-ACS patients. Furthermore, the management of ACS has evolved over the past 12 years since the CRUSADE study in 2005. There have been substantial changes in both medical and procedural management of ACS. Our new results confirm and extend the CRUSADE results in a newer era.

Mechanistically, patients with NSTE-ACS may have expanding myocyte necrosis, but while symptomatically controlled with potent analgesics such as morphine, these agents might be mask symptoms which would otherwise instigate more urgent intervention. In contrast, among STEMI patients, where PCI is routinely performed emergently in all patients, such delays are less likely. Furthermore, recent evidence suggests that morphine may delay and inhibit the absorption of antiplatelet agents,[11,13,14] which may have a more pronounced impact on clinical outcomes in patients not urgently taken to cardiac catheterization. Interestingly, the frequency of coronary thrombus was significantly higher among morphine recipients in the NSTE-ACS cohort with a trend towards significance in the STEMI cohort. It is plausible that inadequate platelet inhibition as a result of morphine administration may have contributed to the higher thrombus rates. As our study was retrospective and observational in nature, these negative outcomes may be explained by associated confounders. However, the association between morphine and increased mortality, infarct size and hospital stay in NSTE-ACS patients was also seen in propensity matched cohorts. Nevertheless, it is impossible to account for all confounding factors with propensity analysis.

Mechanically, it is also plausible that the hemodynamic effects of morphine; reducing heart rate, decreasing blood pressure, and reducing venous return through venodilatation, might be beneficial in STEMI patients, where elevated sympathetic drive can be significant and detrimental.[15] In unadjusted outcomes, mortality rates were lower in STEMI patients who received morphine and our study may have been underpowered to truly assess this clinical endpoint. Supporting this hypothesis, a retrospective study by lakobishvilli et al. using propensity score analysis of 249 matched STEMI pairs, found that the rate of 30-day death was lower in the group that had received morphine (2.4% vs. 6.2%, $P = 0.04$), and this trend persisted after logistic regression analysis (odds ratio 0.40, 95%CI 0.14-1.14, $P = 0.09$).[9] Again such benefit did not extend to the NSTE-ACS cohort in their study. Of the 95 matched NSTE-ACS pairs, no difference was found in the 30-day death rate (2.2% for patients receiving morphine vs. 6.3% in those who did not, $P = 0.16$).[9]

Accordingly, we believe the current ACCF/AHA guidelines provide a sensible guidance to physicians, with morphine sulfate considered the "drug of choice for pain relief" in STEMI patients, albeit without providing a formal class of recommendation.[3] The guidelines provide a Class IIb recommendation (level of evidence B) for the use of morphine sulphate to alleviate pain in patients presenting with NSTE-ACS.[4]

While placebo controlled randomized trials would provide more clarity on morphine's benefit and safety in these cohorts, due to the ethical requirements for analgesia in the control groups, such trials

TABLE 2 Baseline characteristics of NSTE-ACS patients who received morphine compared to those who did not

Characteristics	NSTE-ACS patients who did not receive morphine (*N* = 1316)	NSTE-ACS patients who received morphine (*N* = 424)	*P*-value
Demographics			
Age (years) ± SD	67 ± 13	64 ± 13	0.0005
Female sex, *n* (%)	347 (26)	123 (29)	0.29
BMI (kg/m^2) ± SD	28.7 ± 5.6	28.9 ± 5.8	0.52
Smoker, n (%)	229 (18)	113 (27)	<0.0001
Medical history			
Cerebrovascular disease, *n* (%)	208 (16)	92 (22)	0.005
Peripheral vascular disease, *n* (%)	212 (16)	105 (25)	<0.0001
Chronic lung disease, *n* (%)	177 (13)	55 (13)	0.80
Congestive heart failure, *n* (%)	221 (17)	77 (18)	0.52
Family history of CAD, *n* (%)	290 (22)	97 (23)	0.72
Hypercholesterolemia, *n* (%)	1264 (96)	408 (96)	0.87
Hypertension, *n* (%)	1005 (76)	330 (78)	0.54
Previous CABG, *n* (%)	230 (17)	83 (20)	0.33
Previous PCI, *n* (%)	383 (29)	145 (34)	0.05
Previous MI, *n* (%)	434 (33)	168 (40)	0.01
Diabetes history, *n* (%)	429 (33)	152 (36)	0.22
Creatinine level, (mg/dL) ± SD	1.32 ± 1.30	1.25 ± 0.97	0.26
Prior renal failure, *n* (%)	91 (7)	28 (7)	0.83
Cardiac transplant, *n* (%)	3 (0.2)	2 (0.5)	0.60
Prior valvular surgery, *n* (%)	37 (3)	4 (1)	0.03
Utility of anti-anginal agents (2 weeks prior), *n* (%)	1026 (78)	325 (77)	0.52
Pre-procedure characteristics			
Heart rate, (beat/min) ± SD	70 ± 14	72 ± 14	0.17
Systolic BP (mmHg) ± SD	127 ± 21	125 ± 21	0.06
Diastolic BP (mmHg) ± SD	75 ± 13	75 ± 13	0.65
Oxygen saturation (%) ± SD	95 ± 5	95 ± 4	0.55
Supplemental oxygen given, *n* (%)	1092 (83)	349 (82)	0.01
Thrombolysis pre-procedure, *n* (%)	-	-	-
Shock at start of PCI, *n* (%)	50 (4)	13 (3)	0.48
Cardiac arrest (prior 24 h), *n* (%)	26 (2)	4 (1)	0.16
Door to balloon time, (min) ± SD	119 ± 42	124 ± 98	0.88
Pre-procedural medications			
Beta blockers, *n* (%)	981 (75)	316 (75)	0.19
Calcium channel blockers, *n* (%)	242 (18)	89 (21)	0.17
Nitrates, *n* (%)	202 (15)	70 (17)	0.47
Ranolazine, *n* (%)	12 (1)	12 (3)	0.003
Aspirin, *n* (%)	1198 (91)	383 (90)	0.63
Clopidogrel, *n* (%)	1051 (80)	362 (85)	0.01
Ticagrelor, *n* (%)	196 (15)	47 (11)	0.05
Ticlopidine, *n* (%)	4 (0.2)	-	-
Culprit lesions			
Left main coronary artery	38	19	0.11

(Continues)

TABLE 2 (Continued)

Characteristics	NSTE-ACS patients who did not receive morphine (*N* = 1316)	NSTE-ACS patients who received morphine (*N* = 424)	*P*-value
Left anterior descending artery	394	104	0.03
Circumflex artery	194	70	0.38
Diagonal arteries	44	24	0.03
Marginal arteries	176	66	0.26
Right coronary artery	343	98	0.22
Posterior descending artery	29	13	0.32
Ramus intermedius artery	30	9	0.85
Procedural characteristics			
Technical success rates *n* (%)	1170 (89)	372 (87)	0.43
Procedural success rates *n* (%)	1135 (86)	353 (82)	0.11
Coronary thrombus, *n* (%)	108 (8)	57 (13)	0.002
Post-procedural TIMI 3 flow, *n* (%)	1288 (98)	406 (95)	0.04

BP, blood pressure; BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; MI, myocardial infarction; NSTE-ACS, non-ST elevation acute coronary syndrome; N, patient number; PCI, percutaneous coronary intervention; SD, standard deviation.

are unlikely to be feasible. Thus, a comparison with alternative analgesic approaches are necessary to assess clinical outcomes and are already under investigation, including a Comparison of equimolar oxygen/nitrous oxide mixture (MEOPA) + Paracetamol Versus Morphine Treatment in Acute Coronary Syndrome Analgesia (NCT02198378) and an investigation of the effect of methylnaltrexone on the pharmacokinetic and pharmacodynamic profiles of ticagrelor in patients treated with morphine (NCT02403830). Furthermore, a comparison of oral versus intravenous anti-platelet agents such as cangrelor in patients who require morphine for analgesia would provide useful information to the research community.

4.1 | Study limitations

The most significant limitation of our study is the non-randomized retrospective nature of our investigation. As a result, other unmeasured confounding factors may have influenced the outcomes. An unmeasured factor such as significant chest pain could have influenced morphine administration and also be associated with larger infarct size. However, while the severity of chest pain has been associated with infarct size,[16] such an effect is inconsistent. For example, patients with diabetes mellitus frequently exhibit mild symptoms while infracting large areas of myocardium. Furthermore, the specific cause of death was not recorded in our study. This warrants further investigation as death due to stent thrombosis may

TABLE 3 In-hospital clinical outcomes in STEMI Patients who received morphine compared to those who did not

Outcome	No morphine (*N* = 928)	Morphine (*N* = 359)	Unadjusted OR (95% CI), *P*-value	Adjusted OR[a] (95% CI), *P*-value	Adjusted OR[b] (95% CI), *P*-value
Mortality	7.54%	4.18%	0.53 (0.30-0.95), *P* = 0.03	0.60 (0.34-1.08), *P* = 0.09	0.36 (0.08-1.68), *P* = 0.19
Post-procedural cardiogenic shock	3.13%	1.95%	0.62 (0.27-1.42), *P* = 0.26	0.66 (0.29-1.53), *P* = 0.33	0.56 (0.17-1.78), *P* = 0.32
Post-procedural renal failure	3.77%	1.95%	0.51 (0.22-1.15), *P* = 0.11	0.56 (0.25-1.28), *P* = 0.17	0.55 (0.12-2.59), *P* = 0.45
Length of hospital stay, mean days (SD)	5.91 (8.19)	5.40 (6.93)	*P* = 0.29	*P* = 0.03	*P* = 0.61
Infarct size as measured by troponin, mean ng/mL (SD)	1.29 (3.67)	0.75 (2.38)	*P* = 0.02	*P* = 0.42	*P* = 0.32

CI, confidence interval; N, patient number; OR, odds ratio; PCI, percutaneous coronary intervention; SD, standard deviation; STEMI, ST elevation myocardial infarction.

[a]Adjusted for age and sex.

[b]Adjusted for age, sex, body mass index, family history of coronary artery disease, shock at the start of percutaneous coronary intervention, hypertension, diabetes, smoking status, hypercholesterolemia, heart rate, systolic blood pressure, door to balloon time, prior coronary artery bypass grafting, congestive heart failure, cerebrovascular disease and renal insufficiency.

TABLE 4 In-hospital clinical outcomes in NSTE-ACS patients who received morphine compared to those who did not

Outcome	No morphine (*N* = 928)	Morphine (*N* = 359)	Unadjusted OR (95% CI), *P*-value	Adjusted OR[a] (95% CI), *P*-value	Adjusted OR[b] (95% CI), *P*-value
Mortality	2.51%	3.77%	1.53 (0.83-2.80), *P* = 0.17	1.68 (0.91-3.10), *P* = 0.10	1.58 (0.51-4.92), *P* = 0.43
Post-procedural cardiogenic shock	0.84%	0.71%	0.85 (0.24-3.05), *P* = 0.80	0.88 (0.24-3.17), *P* = 0.84	0.60 (0.06-5.94), *P* = 0.67
Post-procedural renal failure	2.13%	4.25%	2.04 (1.12-3.73), *P* = 0.02	2.22 (1.21-4.07), *P* = 0.01	2.11 (0.80-5.55), *P* = 0.13
Length of hospital stay, mean days (SD)	4.78 (5.25)	6.58 (7.55)	*P* < 0.0001	*P* < 0.0001	*P* < 0.0001
Infarct size as measured by troponin, mean ng/mL (SD)	0.90 (2.16)	1.16 (2.15)	*P* = 0.05	*P* = 0.04	*P* = 0.02

CI, confidence interval; N, patient number; NSTE-ACS, non-ST elevation acute coronary syndrome; OR, odds ratio; PCI, percutaneous coronary intervention; SD, standard deviation.
[a]Adjusted for age and sex.
[b]Adjusted for age, sex, body mass index, family history of coronary artery disease, shock at the start of percutaneous coronary intervention, hypertension, diabetes, smoking status, hypercholesterolemia, heart rate, systolic blood pressure, door to balloon time, prior coronary artery bypass grafting, congestive heart failure, cerebrovascular disease and renal insufficiency.

TABLE 5 In-hospital clinical outcomes by morphine use in propensity matched STEMI patients

Outcome	No morphine (*N* = 107)	Morphine (*N* = 107)	Unadjusted OR (95% CI), *P*-value	Adjusted OR[a] (95% CI), *P*-value	Adjusted OR[b] (95% CI), *P*-value
Mortality	11%	8%	0.73 (0.30-1.81), *P* = 0.49	0.70 (0.28-1.78), *P* = 0.46	0.58 (0.19-1.78), *P* = 0.34
Length of hospital stay, mean days (SD)	7.71 (13.11)	6.98 (10.17)	*P* = 0.65	*P* = 0.61	*P* = 0.81
Infarct size as measured by troponin, mean ng/mL (SD)	1.84 (4.68)	1.11 (2.65)	*P* = 0.21	*P* = 0.22	*P* = 0.67

CI, confidence interval; N, patient number; OR, odds ratio; PCI, percutaneous coronary intervention; SD, standard deviation; STEMI, ST elevation myocardial infarction.
[a]Adjusted for age and sex.
[b]Adjusted for age, sex, body mass index, family history of coronary artery disease, shock at the start of percutaneous coronary intervention, hypertension, diabetes, smoking status, hypercholesterolemia, heart rate, systolic blood pressure, door to balloon time, prior coronary artery bypass grafting, congestive heart failure, cerebrovascular disease and renal insufficiency.

TABLE 6 In-hospital clinical outcomes by morphine use in propensity matched NTE-ACS patients

Outcome	No morphine (*N* = 306)	Morphine (*N* = 306)	Unadjusted OR (95% CI), *P*-value	Adjusted OR[a] (95% CI), *P*-value	Adjusted OR[b] (95% CI), *P*-value
Mortality	2%	5%	2.36 (0.96-5.81), *P* = 0.06	2.32 (0.94-5.78), *P* = 0.07	2.55 (0.95-6.86), *P* = 0.06
Length of hospital stay, mean days (SD)	4.89 (5.36)	6.50 (6.82)	*P* = 0.001	*P* = 0.001	*P* = 0.004
Infarct size as measured by troponin, mean ng/mL (SD)	0.83 (1.49)	1.14 (1.91)	*P* = 0.04	*P* = 0.04	*P* = 0.01

CI, confidence interval; N, patient number; NSTE-ACS, non-ST elevation acute coronary syndrome; OR, odds ratio; PCI, percutaneous coronary intervention; SD, standard deviation.
[a]Adjusted for age and sex.
[b]Adjusted for age, sex, body mass index, family history of coronary artery disease, shock at the start of percutaneous coronary intervention, hypertension, diabetes, smoking status, hypercholesterolemia, heart rate, systolic blood pressure, door to balloon time, prior coronary artery bypass grafting, congestive heart failure, cerebrovascular disease and renal insufficiency.

suggest insufficient platelet inhibition secondary to morphine-induced impaired antiplatelet agent absorption. Additional limitations of our study include the lack of long-term follow up, absence of mechanistic investigation in our study, uncertainty of morphine dosages administered and the limited power of our propensity matched analysis. Finally, although patients with ST depressions in the anterior leads, routinely receive a posterior EKG to assess for a posterior MI in our center, it is possible that some patients with left circumflex coronary artery occlusion were misdiagnosed as an NSTE-ACS when in fact they may have suffered a STEMI.

5 | CONCLUSION

In a large retrospective study, morphine was associated with larger infarct size, a longer hospital stay and a trend towards increased mortality in NSTE-ACS patients but had no adverse effect on in-hospital outcomes in STEMI patients.

6 | CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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Review

Impact of morphine on antiplatelet effects of oral P2Y12 receptor inhibitors

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ABSTRACT

Morphine and P2Y12 receptor inhibitors are both recommended in patients with acute myocardial infarction. Morphine may impede gastrointestinal absorption of several oral drugs including P2Y12 platelet receptor inhibitors.

The aim of this review was to critically discuss drug–drug interactions between oral P2Y12 receptor inhibitors and morphine according to currently available knowledge based on the findings of experimental, observational and randomized clinical studies.

The morphine–clopidogrel pharmacodynamic interaction has been observed in numerous trials and it has been proposed as an explanation for the negative impact of morphine on the clinical outcomes in patients with acute coronary syndromes. An analogous morphine interaction with ticagrelor and prasugrel was found in several observational studies and finally proven in randomized trials in healthy volunteers and acute myocardial infarction patients.

Morphine delays and attenuates exposure and antiplatelet action of oral P2Y12 receptor inhibitors in patients with myocardial infarction. Although this interaction may have potentially harmful consequences, routine avoidance of morphine cannot be recommended until clinically powered trials are completed.

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1. Background

Dual antiplatelet treatment with one of the P2Y12 receptor inhibitors and aspirin is a pivotal therapy in patients with acute coronary syndromes (ACS) [1–4]. According to the current guidelines ticagrelor and prasugrel are preferred in ACS patients undergoing percutaneous coronary intervention (PCI) [3,4].

The rationale for morphine use in patients with acute ischemic chest pain is an expected favorable disease modification [5–7]. The current guidelines for the management of patients with acute myocardial infarction (AMI) continue to recommend intravenous (IV) morphine as the drug of choice for pain relief [3,4]. However, there have never been any randomized clinical trials evaluating the efficacy and safety of morphine in this population, so this recommendation is based solely on expert consensus, not on clinical trial evidence.

Moreover, due to its pharmacological properties, particularly its impact on the gastrointestinal tract, morphine may impede absorption of several orally administered drugs including P2Y12 platelet receptor inhibitors [8].

The aim of this review was to critically discuss drug–drug interactions between oral P2Y12 inhibitors and morphine according to currently available knowledge based on the findings of experimental as well as observational and randomized clinical studies. A search was conducted by two independent investigators (J.K. and A.K.) using PubMed, CENTRAL and Google Scholar databases. No time or language limitations were applied. Proceedings from the Scientific Sessions of the American College of Cardiology (http://www.acc.org), American Heart Association (http://www.heart.org), European Society of Cardiology (http://www.

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escardio.org) were also considered. The following keywords were applied: "morphine" and "clopidogrel", "morphine" and "prasugrel", "morphine" and "ticagrelor", "morphine" and "P2Y12 inhibitors". References of retrieved studies were searched manually for additional studies and reviews.

2. Morphine

The history of opioids is thousands years long. In 1806 Sertürner isolated a pharmacologically active ingredient from a plant and named it morphine after the god of dreams in Greek mythology, Morpheus [9].

The affinity of opioids to G-protein coupled receptors (opioid receptors μ, κ, δ, and opioid receptor like-1 mediating distinctive actions), with subsequent activation of endogenous pain-modulating systems is responsible for the biological effects of morphine [10].

Despite expected relieve of pain and anxiety, morphine also has several potentially harmful side effects. It may cause hypotension, tachycardia as well as bradycardia and respiratory depression [11–13].

The activation of the opioid receptors located in the myenteric plexus and the intestines decreases propulsive motility and secretion of the gastro-intestinal tract. As a result, inhibition of gastric emptying, increase in sphincter tone, induction of stationary motor patterns and blockade of peristalsis ensue [14]. Moreover, nausea and vomiting are also common side effects of morphine (Fig. 1) [6].

Several authors reported impact of morphine on myocardial infarction size [15–19]. In an experimental study, morphine administration before coronary artery occlusion in rats was associated with an increase in myocardial infarction size as assessed by histological techniques 48 h later (45.8% of left ventricular area vs. 35.3%, $p < 0.05$) [15]. On the other hand, an experiment performed on isolated rat hearts showed that morphine given at early reperfusion resulted in a decrease in infarct volume compared to control (9.8 ± 2.5% vs. 30.0 ± 3.7%, $p < 0.001$) [16]. This may be related to the mechanism described by Jang et al. who revealed that activation of the opioid δ receptor results in a cardioprotective effect, by inhibition of mitochondrial permeability transition pore opening [17].

In a single center randomized study the addition of morphine infusion to remote ischemic conditioning (RIC) in ST-segment elevation myocardial infarction (STEMI) patients was associated with a greater percentage of ST-segment resolution and lower peak troponin I levels as compared with RIC alone [18]. These results suggestive of a potentially important role of morphine in ischemic conditioning were supported by observations indicating that the cardioprotective action of ischemic pre-conditioning is blocked by pre-treatment with the opiate receptor blocker naloxone [19]. Nevertheless, studies confirming beneficial clinical effects of morphine in patients with myocardial infarction are lacking. On the contrary, in the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress ADverse Outcomes with Early Implementation of the ACC/AHA guidelines) registry use of morphine either alone or in combination with nitroglycerin for patients presenting with non-ST-segment elevation acute coronary syndromes (NSTE ACS) was associated with higher mortality even after risk adjustment and matching on propensity score for treatment [20]. However, the impact of morphine on short- and long-term prognosis in ACS patients still remains ambiguous [21].

3. Morphine and clopidogrel

In the CRUSADE registry out of 57,039 high-risk patients with NSTE ACS treated with clopidogrel, 17,003 (29.8%) patients received morphine within the first 24 h following hospital presentation [20]. The rates of adverse clinical outcomes were higher in patients who received IV morphine as compared with those who did not. The rate of myocardial infarction was 3.8% vs. 3.0%, death 5.5% vs. 4.7%, and the composite end point of death or myocardial infarction was 8.5% vs. 7.1%. After adjustment for differences in baseline characteristics, the rates of all measured end points, including myocardial infarction (adjusted odds ratio [OR] 1.34, 95% CI 1.22–1.48), death (adjusted OR 1.48, 95% CI 1.33–1.64), and the composite end point of death or myocardial infarction (adjusted OR 1.44, 95% CI 1.34–1.56), remained significantly higher in patients who received IV morphine. The risk of mortality was consistently higher across all measured subgroups and

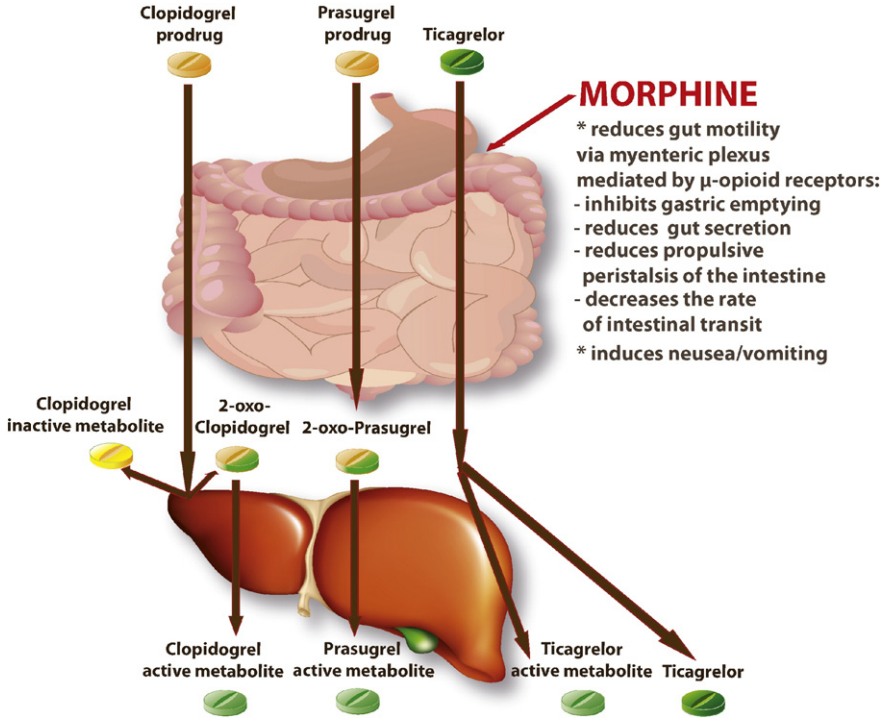

Fig. 1. The possible route of interaction between morphine and P2Y12 receptor inhibitors.

remained present even after evaluation by matched-pairs propensity analysis [20].

Several possible explanations for the higher risk of adverse outcomes in patients who received IV morphine are to be taken into account. Morphine can possibly be a marker for suboptimal medical care. It may indicate sicker patients with ongoing chest pain or with congestive heart failure and its analgesic effects may only serve to blunt the severity of angina without actually ameliorating the underlying pathophysiologic cause of chest pain. Finally, morphine may actually be deleterious to ACS patients [20].

Iakobishvili et al. presented observations from the Acute Coronary Syndrome Israeli Survey 2008, including 765 patients with ST-segment elevation ACS and 993 patients with NSTE ACS treated with clopidogrel. The adjusted outcomes of matched pairs using a propensity score for IV narcotics use tended to be better among patients receiving IV narcotics, however no difference in 95 matched pairs was found in the 30-day death rate (2.2% vs. 6.3%, $p = 0.16$) or 30-day combined end point (15.8% vs. 17.9%, $p = 0.7$). The authors suggested that IV narcotics are safe and perhaps even beneficial, if used appropriately [22].

In another observational study de Waha et al. analyzed the impact of IV morphine administration prior to PCI on ischemic injury and salvaged myocardium assessed by cardiac magnetic resonance imaging in 276 patients with STEMI after 600 mg of clopidogrel. IV morphine administration was associated with larger infarct size, higher extent of microvascular obstruction and lower myocardial salvage index as compared with the non-morphine group (all $p < 0.05$) [23]. These findings remain in line with the results of CRUSADE registry and warrant further randomized clinical trials to assess the effect of IV morphine on clinical outcome.

Zeymer et al. examined the impact of morphine on pharmacodynamics of clopidogrel in 31 STEMI patients treated with primary PCI. The platelet reactivity index (PRI) measured with the VASP assay in subjects on morphine and without morphine at 2 h after intake of the clopidogrel loading dose [LD] was 72.8 ± 15.3% and 60.6 ± 26.1% respectively. After 4 h it amounted 59.1 ± 23.1% and 50.8 ± 24.9% [24].

Despite these inconclusive observations from the Acute Coronary Syndrome Israeli Survey 2008, a strong premise from the CRUSADE registry regarding the harmful effect of morphine, additionally supported by the observations by de Waha et al., cannot be ignored [20,22,23]. There is a biologically plausible cause–effect relationship: opiates inhibit gastric emptying which may delay absorption and decrease peak plasma concentrations of oral drugs [25].

A randomized placebo controlled trial in healthy volunteers showed that co-administration of morphine has a negative impact on clopidogrel pharmacokinetics. Morphine delayed the maximal plasma concentrations of clopidogrel (Tmax: 105 vs. 83 min, $p = 0.025$), reduced the maximal plasma concentrations of clopidogrel active metabolite (Cmax: from 171 vs. 113 ng/mL, $p = 0.025$) and decreased the total exposure assessed by the area under the plasma concentration-time curve by 34% (16,840 vs. 11,103 ng ∗ h/mL, $p = 0.001$). The impact of morphine on the pharmacokinetics of clopidogrel resulted in 2-fold delay in the time required to maximally inhibit platelet aggregation (3 vs. 1.25 h, $p < 0.001$). Residual platelet aggregation remained higher within 1–4 h after morphine injection ($p < 0.005$) [26].

These findings demonstrated a drug–drug interaction between morphine and clopidogrel and provide a potential pathophysiological explanation for the clinical observations from the CRUSADE registry. Hobl et al. concluded that co-administration of morphine and clopidogrel should likely be avoided, if possible. More potent P2Y12-inhibitors may provide greater efficacy when morphine is injected, but their interaction with morphine should be evaluated in further trials [26].

4. Morphine and novel oral P2Y12 inhibitors

The pharmacodynamic evaluation of loading doses of ticagrelor (180 mg) and prasugrel (60 mg) revealed near complete inhibition of ADP induced platelet aggregation, with slightly higher maximal inhibition with prasugrel [27].

Parodi et al. found the following independent predictors of high platelet reactivity (HPR) 2 h after a 180 mg LD of ticagrelor or 60 mg LD of prasugrel: morphine use (OR 5.29, 95% CI 1.44–19.49, $p = 0.012$) and baseline P2Y12 reaction units (PRU) value (OR 1.014, 95% CI 1.00–1.03, $p = 0.046$) [28]. In a subsequent study they confirmed morphine use (OR 4.49, [1.19–16.88], $p = 0.026$) and baseline PRU value (OR 1.015, 95% CI 1.00–1.03, $p = 0.039$) to be predictive of HPR 1 h after a double LD of ticagrelor (360 mg) or regular 60 mg LD of prasugrel [29]. It has been suggested that, in patients with STEMI, drug absorption is crucial to the speed of action of oral antiplatelet agents [29,30]. However caution is needed when interpreting these observations due to the small sample size — the rate of morphine use was identical in both studies and equaled 9 of 25 patients (36%) treated with ticagrelor [28,29]. The authors speculated that the observed biological effect of morphine use is likely related to the inhibition of the normal muscular activity of the stomach and the intestines, which may lead to vomiting or delayed drug adsorption. Thus, intravenous antiplatelet agents such as glycoprotein IIb/IIIa receptor inhibitors or cangrelor should be considered in STEMI patients when early platelet inhibition is required. Both studies provide consistent information suggesting that the onset of action of oral P2Y12 inhibitors may be delayed by co-administration of morphine [28,29].

To corroborate this hypothesis, a multicenter patient-level integrated analysis from 5 observational studies exploring the effect of morphine on platelet reactivity in ticagrelor- or prasugrel-treated STEMI patients undergoing primary PCI was performed [28–33]. Morphine was given according to the decision of attending physicians in the ambulance or in the emergency room. The study was solely pharmacodynamic with use of the VerifyNow assay. Patients who received morphine had higher platelet reactivity at 2 h after the LD of P2Y12 inhibitor (primary end-point) as compared with those without morphine (187.3 vs. 133.7 PRU, $p < 0.001$, respectively). In ticagrelor-treated patients, platelet reactivity 2 h after LD was 231 vs. 110 PRU in those with and without morphine, respectively ($p < 0.001$). Overall, HPR (PRU ≥ 208) at 2 h was found in 53% and 29% patients respectively ($p < 0.001$), without differences between prasugrel and ticagrelor groups. The independent predictors of HPR at 2 h were: morphine use (OR 2.91, 95% CI 1.71–4.97, $p < 0.0001$) and age (OR 1.03, 95% CI 1.01–1.05, $p = 0.010$). Morphine remained significantly associated with HPR (OR 1.89, 95% CI 1.40–2.56, $p < 0.001$) after propensity score adjustment [31].

These data are consistent with observations of Zeymer et al. The PRI measured in 19 STEMI patients on morphine and 12 without morphine at 2 h after the LD of prasugrel was 55.3 ± 31.6 and 42.1 ± 35.4 respectively. After 4 h the difference between groups disappeared (39.5 ± 29.5 vs. 38.5 ± 30.4) [24].

Franchi et al. conducted a post-hoc analysis of a randomized study evaluating escalating loading doses of ticagrelor in 46 patients with AMI treated with PCI. Patients receiving morphine (35%) had increased overall platelet reactivity as assessed by the VerifyNow P2Y12 assay in the first 2 h after LD administration ($p = 0.047$), while no effect was found between 4 to 24 h ($p = 0.78$). Parallel findings were observed with VASP assay. The pharmacokinetic profile tracked pharmacodynamic findings, showing a delay in peak plasma concentrations of both ticagrelor and AR-C124910XX in patients receiving morphine, although the overall drug exposure was similar between groups (receiving and not receiving morphine) [34].

These data are in line with the results of the ATLANTIC (Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery) study [35]. The aim of the ATLANTIC study was to evaluate whether early in-ambulance administration of ticagrelor could safely improve coronary reperfusion in patients with STEMI transferred for primary PCI. The primary end point of ST-segment resolution was significantly improved

with pre-hospital administration of ticagrelor only in patients not receiving morphine ($p = 0.005$ for interaction). It has been proposed that ticagrelor's onset of action may have been delayed due to morphine co-administration in half the study population. The extent to which this interaction may have affected the study results remains unknown [35].

Silvain et al. reported results of the PRIVATE-ATLANTIC, a prespecified substudy of the randomized double blind placebo controlled ATLANTIC trial. The study population consisted of 37 patients, including 22 (59.5%) of whom received morphine before PCI. Morphine administration significantly delayed the response to ticagrelor as assessed by VASP-PRI, with a significant difference at 1 h after PCI (22.9% vs. 83.2%, $p = 0.003$) and 6 h after the loading dose (10.9% vs. 37.6%, $p = 0.003$). This effect was more pronounced in the pre-hospital than in the in-hospital ticagrelor group: 28.5% vs. 82.3%, $p = 0.052$ at the end of PCI procedure; 15.7% vs. 69.1%, $p = 0.006$ at 1 h after PCI; and 6.8% vs. 40.9%, $p = 0.02$ at 6 h after the loading dose. This observation supports the hypothesis of an interaction between morphine and oral P2Y12 inhibitors and may account for the neutral effect of prehospital treatment on the primary endpoint in ATLANTIC [36].

Morton et al. performed an open-label, crossover, randomized study aimed to determine whether morphine delays the onset of action of prasugrel in patients with previous primary PCI for STEMI. Patients were randomly assigned to receive either morphine 5 mg or saline intravenously followed by 60 mg prasugrel. The platelet reactivity, assessed by the VerifyNow P2Y12 assay were 26 ± 36 PRU with saline and 104 ± 110 PRU with morphine ($p = 0.027$) 2 h after administration of prasugrel. The response to 20 μM of ADP evaluated with light transmittance aggregometry (LTA) was 5 ± 12% with saline and 23 ± 28% with morphine ($p = 0.033$) at 2 h from baseline. These differences in platelet reactivity disappeared after 24 h (20 ± 27 PRU saline vs. 19 ± 29 PRU morphine). The low number of patients ($n = 11$) who completed the study and lack of pharmacokinetic data are its major limitation. The authors concluded that morphine delays prasugrel's onset of action. Therefore, intravenous drugs may be necessary to reduce the risk of acute stent thrombosis in morphine-treated STEMI patients undergoing primary PCI [37].

The existing body of evidence supports the hypothesis of drug–drug interaction when morphine and ticagrelor or prasugrel are co-administered, but until recently there were no data from randomized combined pharmacokinetic–pharmacodynamic studies in AMI patients to confirm these alleged interactions.

The IMPRESSION study was the first randomized study to confirm negative impact of morphine on pharmacokinetics and antiplatelet effects of a novel P2Y12 receptor inhibitor (ticagrelor) in AMI patients. The IMPRESSION study was a single center, randomized, double-blind, placebo-controlled trial that assessed the influence of morphine on the pharmacokinetics and pharmacodynamics of ticagrelor in 70 patients with AMI [38]. Morphine infusion lowered the total exposure to both ticagrelor and its active metabolite (AR-C124910XX) within the first 12 h after administration of the 180 mg ticagrelor LD as compared with placebo ($AUC_{(0-12)}$ of ticagrelor: 6307 ± 4359 vs. 9791 ± 5136 ng ∗ h/mL; corresponding to a difference of 36%; $p = 0.003$; $AUC_{(0-12)}$ for AR-C124910XX: 1503 ± 1138 vs. 2388 ± 1555 ng ∗ h/mL; difference: 37%; $p = 0.008$) [39]. The maximal plasma concentrations of ticagrelor in patients receiving morphine were delayed by 2 h as compared with placebo and reduced (C_{max} for ticagrelor: 1156 ± 771 vs. 1683 ± 847 ng/mL; $p = 0.006$). Morphine administration and the presence of ST-segment elevation myocardial infarction were independent predictors of low $AUC_{(0-12)}$ values in multiple regression analysis. After adjustment for AMI type (STEMI vs. NSTEMI), a mean decrease in $AUC_{(0-12)}$ of 3236 ± 1101 ng ∗ h/mL was found in morphine-treated patients as compared with the placebo group ($p = 0.005$). Assessment of platelet reactivity showed stronger antiplatelet effect in the placebo group than in morphine-treated patients [39]. In consequence, the prevalence of HPR, indicating increased risk of ischemic complications [40], was higher in the morphine group in the majority of the measurement points, with the most pronounced difference between 0.5 and 4 h after administration of the LD of ticagrelor. Hence, the observed reduction in the antiplatelet effect of ticagrelor was considered to be

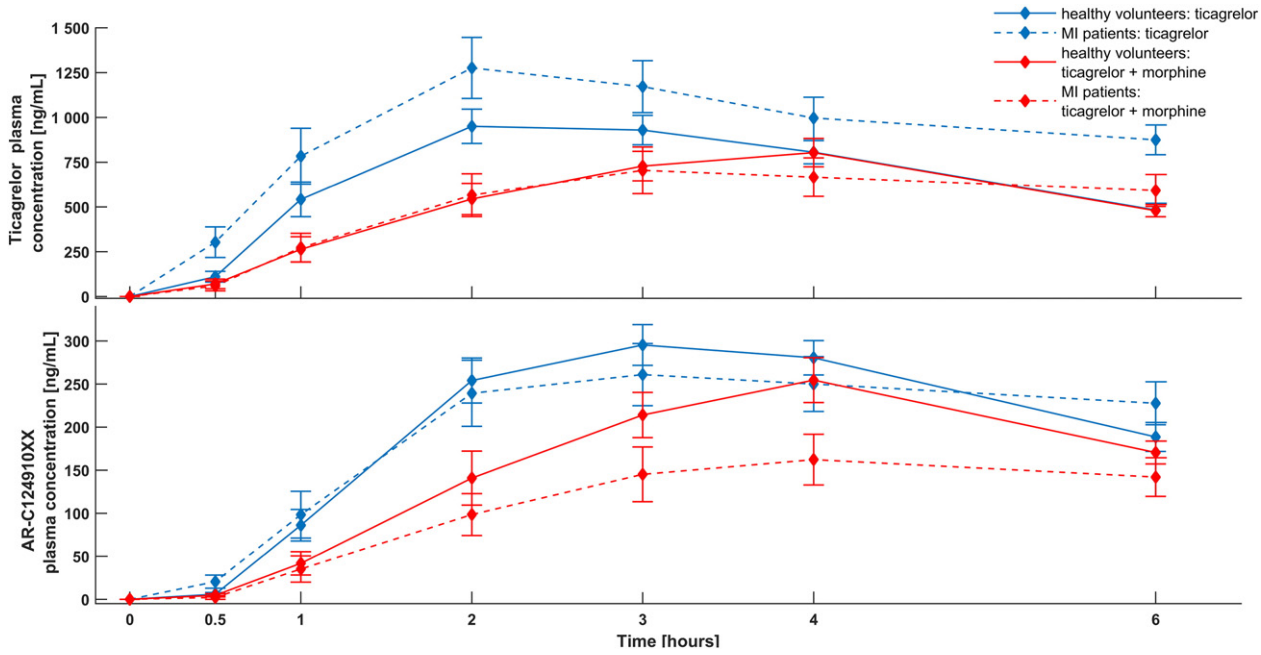

Fig. 2. Plasma concentrations of ticagrelor and AR-C124910XX in healthy volunteers and in patients with myocardial infarction. Plasma concentrations of ticagrelor (upper panel) and AR-C124910XX (lower panel) after oral administration of a 180 mg ticagrelor loading dose, with (red) or without (blue) following intravenous injection of morphine in patients with myocardial infarction and healthy volunteers. Superimposed data from two randomized studies [39,42]. Data present means ± standard error of the mean.

clinically relevant [39]. Although the underlying mechanism of these findings was not investigated in detail, it seems most likely that morphine impairs absorption of ticagrelor [39]. Moreover in the sub-analysis of the IMPRESSION study, we did not find any evidence that the extent of ticagrelor conversion to AR-C124910XX is affected by morphine administration [41]. Decreased exposure to AR-C124910XX in the morphine arm compared with the placebo arm of the study was most likely caused by a proportional attenuation of exposure to the parent drug.

A recent randomized controlled trial in healthy volunteers generally confirmed the IMPRESSION findings [42]. Morphine injection delayed maximal plasma concentrations of ticagrelor by 1 h and AR-C124910XX by 2 h. This was associated with reduction of maximal plasma concentrations of ticagrelor (from 1222 to 913 ng/mL, $p = 0.015$) and AR-C124910XX (from 325 to 242 ng/mL, $p = 0.028$), and the total exposure as measured by the AUC_{0-n} by 22% ($p = 0.011$) for ticagrelor and 23% ($p = 0.009$) for its active metabolite. However, the impact of morphine on ticagrelor's pharmacodynamics was not reflected by a similar pharmacodynamic effect assessed by whole blood aggregometry and platelet plug formation under high shear rates. Of note, both assays were maximally affected by approximately 50% of maximal concentrations of ticagrelor. This observation suggests that a 180 mg ticagrelor LD may be potent enough to at least partially overcome the interaction between oral P2Y12 inhibitors and morphine in stable setting [42], but not in AMI patients according to results of the IMPRESSION study [39].

Superimposition of concentration curves from these two randomized studies [39,42] shows general agreement between healthy volunteers and AMI patients regarding plasma concentration of ticagrelor and AR-C124910XX. However, considerably higher plasma concentrations of ticagrelor were observed in AMI patients without morphine while in healthy volunteers' concentrations of AR-C124910XX were higher in subjects receiving ticagrelor and morphine (Fig. 2). On the other hand, as evidenced by the curves of ADP-induced platelet aggregation, platelet inhibition in healthy volunteers was definitely stronger and largely independent of morphine. On the contrary, in AMI patients the pharmacodynamic effect of ticagrelor was markedly less pronounced when morphine was co-administered (Fig. 3). As plasma concentrations of ticagrelor were similar between healthy subjects and patients with AMI 2 h after co-administration with morphine, patients with AMI appear to require higher levels of ticagrelor, likely due to their enhanced platelet activation [43] (Figs. 2 and 3).

In a further randomized, controlled trial in healthy volunteers, morphine reduced maximal plasma concentrations of prasugrel active metabolite by 31% ($p = 0.019$), but neither decreased drug exposure nor altered platelet inhibition [44].

However, results in healthy volunteers may underestimate the true effect of morphine in patients suffering from myocardial infarction possibly because of their reduced gastrointestinal perfusion or their enhanced platelet activation.

5. Clinical implications of morphine–P2Y12 receptor inhibitors' interaction

The morphine–P2Y12 receptor inhibitors' interaction observed in numerous trials (Table 1) warrants prompt investigation in clinically powered randomized trials in the AMI setting. Although the interaction may potentially lead to harmful consequences, routine avoidance of morphine cannot be recommended until such trials are completed. Moreover, there is a need to evaluate alternative strategies overcoming or at least diminishing the negative impact of morphine on the antiplatelet effect of oral P2Y12 receptor inhibitors in AMI patients including: use of cangrelor, a novel IV P2Y12 receptor inhibitor, or concomitant administration of a glycoprotein IIb/IIIa receptor inhibitor, use of a prokinetic agent (e.g., metoclopramide), administration of crushed ticagrelor tablets and replacement of morphine by a short-acting analgesic, alfentanil [5,45–47].

6. Conclusions

Morphine delays and attenuates exposure and action of oral P2Y12 receptor inhibitors in patients with myocardial infarction. There is a need of further adequately powered randomized trials investigating the impact of morphine on clinical endpoints in the AMI setting.

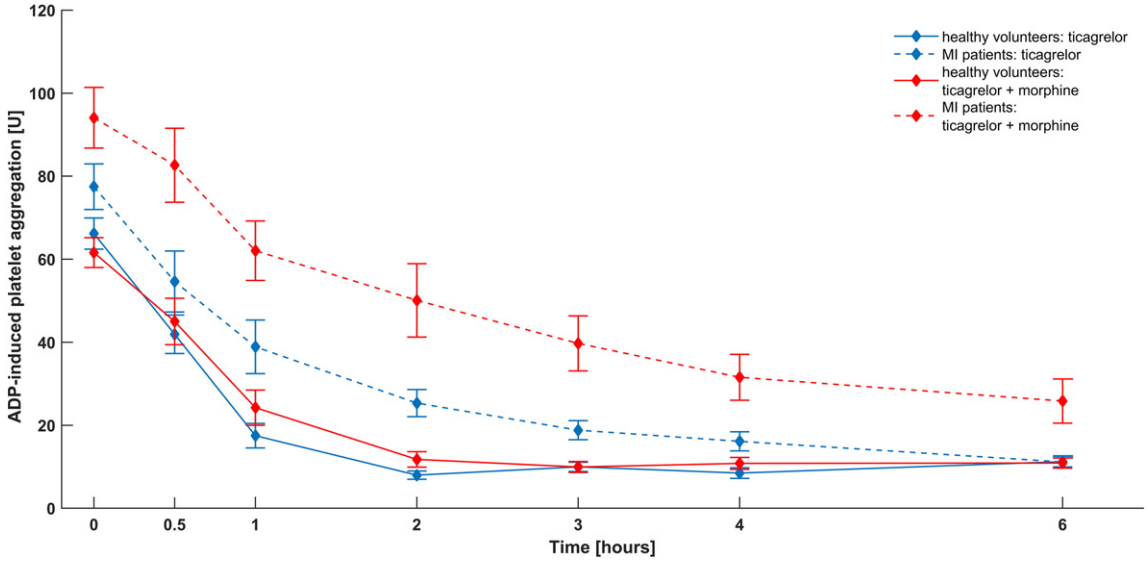

Fig. 3. Platelet reactivity after loading dose of ticagrelor in healthy volunteers and in patients with myocardial infarction. ADP-induced platelet aggregation after oral administration of a 180 mg ticagrelor loading dose, with (red) or without (blue) following intravenous injection of morphine in patients with myocardial infarction and healthy volunteers. Superimposed data from two randomized studies [39,42]. Data present means ± standard error of the mean.

Table 1
Studies regarding morphine–P2Y12 receptor inhibitors' interaction [20,22–24,26,28,29,31,34–37,39,42,44].

Author/acronym	Type of the study	Aim of the study	Study population	P2Y12 inhibitor on morphine	Decision regarding morphine	Results regarding interaction P2Y12 inhibitor–morphine
Meine TJ/CRUSADE	Retrospective, observational registry, not focused on morphine	Evaluation of acute medications and interventions, in-hospital outcomes, and discharge treatments.	n = 57039 NSTE ACS	Clopidogrel n = 17,003 (30%)	According to the physician's decision	Suspected negative impact on clinical outcome.
Iakobishvili Z/ACSIS	Retrospective, observational registry, focused on morphine.	Evaluation of the effect of prehospital and in-hospital IV narcotics use on the in-hospital and 30-day outcomes among consecutive patients with various types of ACS.	n = 765 STEMI; n = 993 NSTE ACS	Clopidogrel n = 261(34%) STEMI; n = 97 (10%) NSTE ACS	According to the physician's decision	Neutral regarding clinical outcome
Parodi G/RAPID	Randomized not regarding morphine	To compare the action of prasugrel and ticagrelor in STEMI patients undergoing primary PCI.	n = 50 STEMI	Ticagrelor n = 9 (36%), prasugrel n = 12 (48%)	According to the physician's decision	Suspected negative impact on pharmacodynamics of ticagrelor and prasugrel.
Morton AC	Randomized regarding morphine, open-label, crossover study	To determine whether morphine delays the onset of action of prasugrel in patients with previous PPCI for STEMI.	n = 11 post-STEMI	Prasugrel n = 11 (100%)	Randomization	Negative impact on pharmacodynamics of prasugrel.
Hobl EL	Randomized regarding morphine, double-blind, placebo-controlled, cross-over trial	To examine possible drug–drug interaction between clopidogrel and morphine.	n = 24 healthy subjects	Clopidogrel n = 24 (100%)	Randomization	Negative impact on pharmacokinetics and pharmacodynamics of clopidogrel.
Parodi G/RAPID 2	Randomized not regarding morphine	To evaluate the impact of increased ticagrelor LD on platelet inhibition as compared with the standard prasugrel LD.	n = 50 STEMI	Ticagrelor n = 9 (36%), prasugrel n = 13 (54%)	According to the physician's decision	Suspected negative impact on pharmacodynamics of ticagrelor and prasugrel.
Parodi G	Patient-level integrated analysis of 5 studies regarding morphine	Assessment of platelet inhibition after LD of prasugrel/ticagrelor according to morphine use.	n = 300 STEMI	Ticagrelor n = 62 (30%), prasugrel n = 33 (35%)	According to the physician's decision	Suspected negative impact on pharmacodynamics of ticagrelor and prasugrel.
Montalescot/ATLANTIC	Randomized not regarding morphine	To assess whether prehospital administration of ticagrelor can improve coronary reperfusion and clinical outcome.	n = 1862 STEMI	Ticagrelor n = 800 (43%)	According to the physician's decision	Suspected negative impact on clinical surrogate end-point.
de Waha S	Observational, focused on morphine.	To analyze the impact of IV morphine on ischemic injury and salvaged myocardium assessed by cardiac magnetic resonance imaging in patients with STEMI reperfused by PPCI.	n = 276 STEMI	Clopidogrel n = 123 (45%)	According to the physician's decision	Suspected negative impact on clinical surrogate end-point.
Franchi F	Randomized not regarding morphine, post-hoc analysis focused on morphine	To assess the impact of morphine on pharmacokinetic profiles of ticagrelor.	n = 46 AMI	Ticagrelor n = 16 (35%)	According to the physician's decision	Suspected negative impact on pharmacokinetics and pharmacodynamics of ticagrelor.
Silvain J/PRIVATE-ATLANTIC	Randomized not regarding morphine, prespecified substudy	To evaluated the impact of morphine administration on pharmacodynamic and pharmacokinetic effect of ticagrelor pretreatment	n = 37 STEMI	Ticagrelor n = 22 (59%)	According to the physician's decision	Suspected negative impact on pharmacodynamics of ticagrelor.
Zeymer U/ETAMI	Randomized not regarding morphine	To investigate the influence of morphine on platelet inhibition with clopidogrel and prasugrel in patients with primary PCI	n = 62 STEMI	Clopidogrel n = 13 (42%), prasugrel n = 19 (61%)	According to the physician's decision	Negative impact on pharmacodynamics of clopidogrel and prasugrel.
Kubica J/IMPRESSION	Randomized regarding morphine, double-blind, placebo-controlled study	To assess the influence of IV morphine on the pharmacokinetics and pharmacodynamics of ticagrelor and its active metabolite in AMI patients	n = 70 AMI	Ticagrelor n = 35 (50%)	Randomization	Negative impact on pharmacokinetics and pharmacodynamics of ticagrelor.
Hobl EL	Randomized regarding morphine, double-blind, placebo-controlled, cross-over trial	To examine drug–drug interaction between morphine and ticagrelor.	n = 24 healthy subjects	Ticagrelor n = 24 (100%)	Randomization	Negative impact on pharmacokinetics and neutral on pharmacodynamics of ticagrelor.
Hobl EL	Randomized regarding morphine, double-blind, placebo-controlled, cross-over trial	To examine drug–drug interaction between morphine and prasugrel.	n = 12 healthy subjects	Prasugrel n = 12 (100%)	Randomization	Negative impact on pharmacokinetics and neutral on pharmacodynamics of prasugrel.

ACS, acute coronary syndromes; AMI, acute myocardial infarction; IV, intravenous; LD, loading dose; NSTE ACS, non-ST elevation acute coronary syndrome; NSTEMI, non-ST elevation myocardial infarction; PCI, percutaneous coronary intervention; PPCI, primary percutaneous coronary intervention; STEMI, ST elevation myocardial infarction.

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$P2Y_{12}$ Receptor Antagonists and Morphine
A Dangerous Liaison?

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Abstract—$P2Y_{12}$ 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 $P2Y_{12}$ 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

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$P2Y_{12}$ 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 $P2Y_{12}$ receptor antagonists, as well as on the central issue of whether such interactions may underlie clinically significant effects on patient outcomes.

$P2Y_{12}$ 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 al[8] 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 $P2Y_{12}$ 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

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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 ≤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 nonsignificant 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 $P2Y_{12}$ 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 ≈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 $P2Y_{12}$ 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 $P2Y_{12}$ 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

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Table. Studies on the Effect of Morphine on $P2Y_{12}$ 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 Tmax, Cmax 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, $P2Y_{12}$ 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.

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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 ≈40% of patients were treated with a $P2Y_{12}$ 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

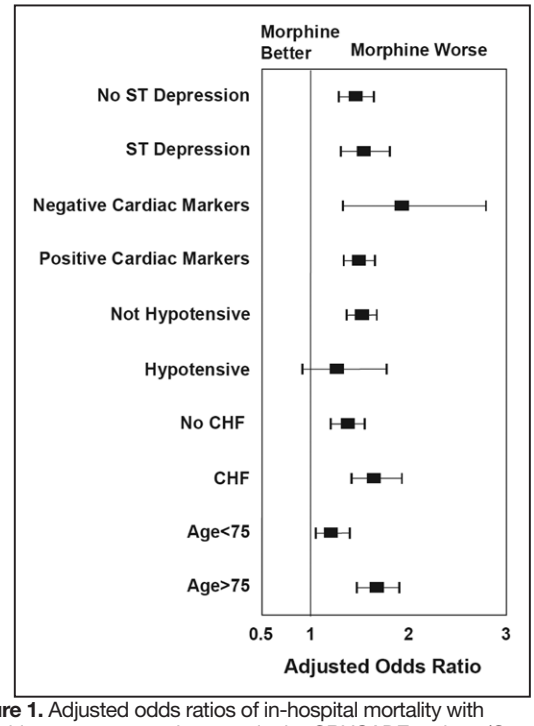

Figure 1. Adjusted odds ratios of in-hospital mortality with morphine use across subgroups in the CRUSADE registry (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines). CHF indicates chronic heart failure. Reproduced from Meine et al[24] with permission. Copyright ©2005, Elsevier.

(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 $P2Y_{12}$ 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 $P2Y_{12}$ 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 ticagrelor[30] 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 $P2Y_{12}$ 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 ACS[32] and was associated with perioperative cardioprotection (in terms of preservation of contractile function[33] and reduced cardiac biomarker release[34]) 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 $P2Y_{12}$ 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

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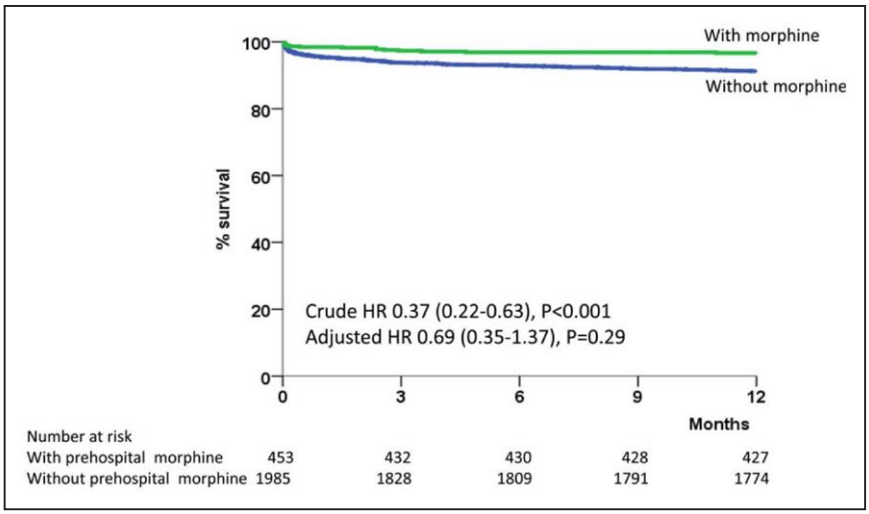

Figure 2. One-year survival according to morphine use in the FAST-MI 2010 cohort (French Registry of Acute Coronary Syndrome). HR indicates hazard ratio. Reproduced from Puymirat et al[26] with permission. Copyright ©2016, Oxford University Press.

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 $P2Y_{12}$ 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 $P2Y_{12}$ 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 $P2Y_{12}$ receptor antagonists should be a careful benefit-over-harm ratio–considering choice.

Disclosures

None.

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$P2Y_{12}$ Receptor Antagonists and Morphine: A Dangerous Liaison?

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

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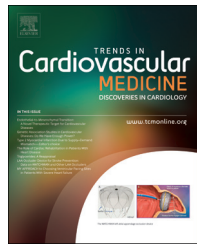

Time-honored treatments for the initial management of acute coronary syndromes: Challenging the status quo

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A B S T R A C T

Morphine, oxygen, and nitrates are time-honored therapies for the initial management of acute coronary syndrome (ACS). The traditional goal of these agents in ACS has been to (1) relieve symptoms, (2) prevent infarction or limit its size, and (3) improve outcomes, both acutely and during follow-up. Despite their ongoing use in routine ACS care, nitrates, morphine, and oxygen have no evidence of clinical outcomes benefit from randomized trials. Furthermore, emerging data have recently suggested that, in certain situations, morphine and oxygen may actually be associated with harm in the setting of ACS. In this review article, we thoroughly examine updated evidence for each of these acute-phase ACS agents with respect to their individual risks and benefits. We review guideline recommendations for these therapies and outline future directions for their use in clinical practice.

Key words: Morphine, Oxygen, Nitrates.

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Introduction

The use of morphine, oxygen, nitrates, and aspirin is often recommended as first-line therapy in patients with acute coronary syndromes (ACS). This strategy has often been summarized as "MONA" in many textbooks, websites, and in US teaching hospitals and medical training institutions that follow the UK tradition [1–10]. The traditional goal of these acute-phase ACS agents has been to (1) relieve symptoms, (2) prevent infarction or limit its size, and (3) improve outcomes, both acutely and during follow-up. However, emerging data have recently challenged the routine administration of these therapies in ACS. For example, morphine has been associated with increased mortality when administered to non-ST elevation myocardial infarction (NSTEMI) patients in observational cohorts, with mechanistic research further suggesting that morphine delays the gastrointestinal absorption of antiplatelet therapy [11,12]. In addition, oxygen has been associated with increased infarct size and arrhythmias when administered to non-hypoxic patients [13]. The data for nitrates are consistently inconclusive. Therefore, of the four common therapies administered in the initial management of ACS patients, aspirin is the only one with high-quality evidence for benefit. In this narrative review, we will examine the utility of morphine, oxygen, and nitrates in ACS, including the potential benefits and harmful effects of each, and reflect on the future of these agents in clinical practice.

Morphine

Morphine was recognized as a useful analgesic in the management of ACS as far back as 1930 [14]. Since then it has become the standard treatment for ACS patients with severe chest pain, with endorsements from the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) and the European Society of Cardiology (ESC) [15,16]. However, concerns about morphine use have emerged over the past decade due to an observational association with adverse clinical outcomes in NSTEMI patients and a delay in the absorption of oral anti-platelet agents; placing its routine use under closer scrutiny [11,17–19] (Table 1).

Current guidelines

The ESC guidelines for the management of ST segment elevation myocardial infarction (STEMI), published in 2012, provide a Class 1 (level of evidence C) recommendation for morphine utility in STEMI patients (Table 2) [20]. In contrast, 2015 ESC NSTEMI guidelines, recommend morphine exclusively in the context of resistant chest pain after nitrate and beta blocker therapy administration and provide no formal class of recommendation [21].

The 2013 ACCF/AHA guidelines provide no formal class of recommendation or level of evidence designation for the utility of morphine in STEMI patients. However, they state that "In the absence of a history of hypersensitivity, morphine sulfate is the drug of choice for pain relief in patients with ST-segment elevation MI (STEMI)", as, "it can alleviate the work of breathing, reduce anxiety, and favorably affect ventricular loading conditions" [22]. The 2014 ACCF/AHA Guidelines for the Management of Patients with Non–ST-Elevation Acute Coronary Syndromes, provide a Class 2b recommendation (level of evidence B) for morphine administration in this cohort [23].

Benefits

Analgesia

Chest pain is the most common presenting complaint in ACS [24]. Analgesic options in this cohort remain limited and there have been few comparative trials. Morphine is the standard in ACS patients with pain refractory to beta blockers or nitrates. To take one example, in the Metoprolol-Morphine (MEMO) trial, among 265 adults with suspected or definite MI, morphine offered faster and more effective analgesia than metoprolol [25].

Hemodynamic effects

Morphine decreases heart rate, blood pressure, and venous return [26]. These effects appear to reduce myocardial oxygen demand during ACS. However, this hypothesis is only supported by two studies [26,27]. Unfortunately, both studies are limited by small numbers and neither occurred in the setting of ACS.

Concerns

Clinical outcomes

In 2005, a retrospective observational analysis of 57,039 NSTEMI patients found that morphine recipients had a significantly higher incidence of ST depression and positive cardiac biomarkers [11]. Furthermore, morphine recipients had a significantly higher likelihood of recurrent MI (odds ratio = 1.34), death (OR = 1.48), and the composite end point of both (OR = 1.44) [11]. Subsequently, de Waha et al. [28] reported that STEMI patients who received morphine were more likely to have a larger infarct and reduced myocardial salvage indices on cardiac MRI.

In contrast, two other, albeit smaller, observational studies failed to demonstrate adverse outcomes with morphine use in ACS [29,30]. Iakobishvili et al. used a propensity score to match 249 STEMI pairs and found that the rate of 30-day mortality appeared lower in those who received narcotics (2.4% vs. 6.2%, $p = 0.04$), with no statistically significant difference in outcomes between 95 matched NSTE-ACS patients ($p = 0.16$) [29]. Puymirat et al. [30] found that, after adjustment for baseline differences, a composite of in-hospital complications and 1-year survival (hazard ratio = 0.69; 95% confidence interval: 0.35–1.37) was not increased with pre-hospital morphine use in 2438 STEMI patients. After propensity score matching, 1-year survival according to pre-hospital morphine was also similar. However, in this study, the rate of non-fatal recurrent MI was higher in patients pre-treated with morphine (1.8 vs. 0.7%, $p = 0.03$) [30].

Interaction with anti-platelet agents

New data suggest that morphine may inhibit and delay the absorption of oral anti-platelet agents. This off-target effect

Table 1 – The benefits and concerns of morphine in acute myocardial infarction.

	Form of evidence	Summary	References
Benefits			
Pain relief	Randomized controlled trial	Morphine provides superior and faster chest pain relief to metoprolol.	[25]
Hemodynamic benefits	Observational studies	Morphine decreases heart rate, blood pressure, and venous return.	[26,27]
Concerns			
Clinical outcomes	Observational studies	Observational evidence in 2005 suggested morphine is associated with increased mortality (OR = 1.48) and recurrent infarct (1.34) in NSTE-ACS patients. Subsequent observational studies have challenged this finding.	[11,28–30]
Absorption of oral anti-platelet agents	Observational studies and a randomized controlled trial	Multiple small observational studies and one randomized controlled trial have demonstrated that morphine delays and reduces the GI absorption of anti-platelet agents.	[12,17,18,31,32]

could theoretically account for the increase in adverse outcomes reported among NSTE-ACS patients [11]. Initial studies on this topic involved healthy adults randomized to morphine or placebo. Hobl et al. [17] demonstrated that morphine delayed clopidogrel absorption (T_{max} = 105 vs. 83 min, p = 0.025), while also reducing the total exposure of its active metabolites by 34% (p = 0.001). Morphine also delayed the maximal inhibition of platelet aggregation by 2 h (n = 24; $p < 0.001$) [17]. Similar results were seen with ticagrelor and prasugrel [31,32]. These results have also been corroborated by larger observational studies in STEMI patients [18].

Lending further support to this theory is a recent trial of 70 STEMI patients evaluating surrogate outcomes [12]. Morphine lowered the total exposure to ticagrelor and its active metabolite by 36%, with a concomitant delay in maximal plasma concentration of ticagrelor (4 vs. 2 h; p = 0.004) and an increase in 2-hour residual platelet reactivity. There were some limitations to this trial [12]. For example, patients with "unbearable chest pain" and "patients who request analgesia" were excluded, arguably the cohort of patients most in need of morphine in "real-world" practice.

Suggestions and future directions

Given the limited benefit, association with increased mortality, and interactions with antiplatelet medications, we advise that morphine should only be used judiciously in the setting of ACS. The evidence to date suggesting that morphine is harmful in ACS patients is based primarily on a large retrospective observational study and studies evaluating surrogate outcomes [11,12]. While this association persisted in propensity-matched outcomes, this methodology is imperfect and it is impossible to account for all confounders including severity of chest pain. Unfortunately, the gold standard assessment—a placebo-controlled randomized clinical trial—may not be feasible with current treatment options due to the ethical requirement for appropriate analgesia in control groups. Further scholarly efforts, in the form of

Table 2 – ACCF/AHA and ESC Guidelines for the utility of morphine in the management of ACS.

	Class of recommendation	LOE
NSTEMI		
AHA/ACCF		
2014	Class 2b: In the absence of contraindications, it may be reasonable to administer morphine sulfate intravenously to patients with NSTE-ACS if there is continued ischemic chest pain despite treatment with maximally tolerated anti-ischemic medications.	B
ECS		
2015	No formal recommendation given. However, the committee advise that morphine be administered exclusively in the context of resistant chest pain after nitrate and beta blocker therapy administration.	
STEMI		
AHA/ACCF		
2013	No formal recommendation given. However, the committee advise that in the absence of history of hypersensitivity, morphine sulfate is the drug of choice for pain relief in this cohort.	
ESC		
2012	Class 1: Relief of pain is of paramount importance, not only for humane reasons but because the pain is associated with sympathetic activation that causes vasoconstriction and increases the workload of the heart. Titrated intravenous opioids (e.g., morphine) are the analgesics most commonly used in this context.	C

ACCF, American College of Cardiology Foundation; ACS, acute coronary syndrome; AHA, American Heart Association; ESC, European Society of Cardiology; LOE, level of evidence; NSTEMI, non-ST segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

randomized clinical trials, evaluating alternative strategies to explore these concerns would be valuable, including investigation of intravenous anti-platelet agents such as cangrelor in patients requiring morphine for ACS [33]. In addition, alternative analgesic approaches are under investigation, including a Comparison of equimolar oxygen/nitrous oxide mixture (MEOPA) + Paracetamol Versus Morphine Treatment in Acute Coronary Syndrome Analgesia (NCT02198378), which is underway in Toulouse, and an investigation of the effect of methylnaltrexone on the pharmacokinetic and pharmacodynamic profiles of ticagrelor in patients treated with morphine (NCT02403830).

Oxygen

Oxygen has been used in the management of ACS since 1900 [34]. Its widespread utility was based on the belief that oxygen supplementation can improve myocardial oxygenation and reduce infarct size (Table 3). However, there is evidence suggesting that oxygen therapy may be detrimental in normoxic STEMI patients [13] and its utility in ACS has recently been debated [35]. Despite this, oxygen use remains common. For example, in a 2010 survey of 524 UK health care providers, 98.3% of respondents said they usually or always use oxygen in the treatment of ACS, with 55% believing oxygen definitely or probably reduces the risk of death [36].

Guidelines

The current ESC STEMI guidelines recommend oxygen administration to those who are breathless, hypoxic, or who have heart failure (Table 4) [20]. The ESC NSTEMI patients state that oxygen should be administered when blood oxygen saturation is <90% or if the patient is in respiratory distress [21].

The ACCF/AHA 2013 STEMI guidelines state that oxygen therapy is appropriate for patients who are hypoxemic (oxygen saturation <90%) and acknowledge the need for more research on its utility in ACS patients [22]. The 2014 AHA/ACC NSTEMI guidelines provide a Class 1 level C recommendation for oxygen therapy in patients with an oxygen saturation <90% and in patients with respiratory distress, or other high-risk features of hypoxemia [37]. This was a change from the 2007 UA/NSTEMI guidelines that recommended the routine administration of supplemental oxygen to all patients with NSTE-ACS during the first 6 h after presentation on the premise that it is safe and may alleviate hypoxemia [38].

Benefits

Increased tissue oxygen transport in hypoxic patients

Few would argue against the use of oxygen in hypoxic ACS patients, but, surprisingly, there is a dearth of studies examining this question. A 1969 study demonstrated that in patients with an arterial oxygen saturation of less than 90%, oxygen administration increased cardiac output, oxygen content, and tissue oxygen transport, with a variable effect on peripheral vascular resistance [39].

ST elevation resolution

In a small clinical study of 17 patients with anterior STEMI, 15 L/min oxygen via facemask resulted in a fourfold increase of PaO_2 and lowered ST-segment elevation by 16% [40].

Concerns

Hemodynamic effects

A study in healthy volunteers demonstrated that oxygen therapy decreased cardiac output by 10% and left ventricular myocardial perfusion by 23% as assessed by MRI [41]. The authors attributed the decrease in cardiac output to a lower

Table 3 – The benefits and concerns of oxygen in acute myocardial infarction.

	Form of evidence	Summary	References
Benefits			
Reduction in ST elevation	Non-randomized controlled trial	A small clinical study suggested oxygen therapy reduces ST elevation by 16%.	[40]
Increased cardiac output	Observational study	Oxygen increased cardiac output in patients with a 0_2 saturation of ≤90%.	[39]
Concerns			
Hemodynamic effects	Observational studies	In ACS patients whose arterial oxygen saturation was over 90%, oxygen administration lowered cardiac output, decreased coronary blood flow, and increased coronary vascular resistance.	[39,41]
Clinical outcomes	Meta-analysis of randomized controlled trials	Meta-analysis suggests oxygen has a relative risk of death of 2.05 (95% CI: 0.75–5.58) in patients with acute myocardial infarction.	[44]
Recurrent myocardial infarct	Randomized controlled trial	The AVOID trial demonstrated an increase in the rate of recurrent myocardial infarction in non-hypoxic patient who receive oxygen therapy (5.5%vs. 0.9%, $p = 0.006$).	[13]
Arrhythmia	Randomized controlled trial	In the AVOID trial, oxygen therapy was associated with increased frequency of cardiac arrhythmia (40.4% vs. 31.4%; $p = 0.05$).	[13]
Infarct size	Randomized controlled trial	The AVOID trial demonstrated an increase in infarct size at 6 months in non-hypoxic patients who received oxygen therapy as measured by cardiac MR. ($n = 139$; 20.3 vs. 13.1 g; $p = 0.04$).	[13]

Table 4 – ACCF/AHA and ESC Guidelines for the utility of oxygen in the management of ACS.

	Class of recommendation	LOE
NSTEMI		
AHA/ACCF		
2014	Class 1 recommendation for oxygen therapy in patients with an oxygen saturation <90% and in patients with respiratory distress, or other high-risk features of hypoxemia.	C
ECS		
2015	No formal recommendation given. However, the committee advise that oxygen should be administered when blood oxygen saturation is <90% or if the patient is in respiratory distress.	
STEMI		
AHA/ACCF		
2013	No formal recommendation given. However, the committee advise that oxygen therapy is appropriate for patients who are hypoxemic (oxygen saturation <90%) and acknowledge the need for more research on its utility in ACS patients.	
ESC		
2012	No formal recommendation is provided. However, the committee recommend oxygen administration to those who are breathless, hypoxic, or who have heart failure.	

ACCF, American College of Cardiology Foundation; ACS, acute coronary syndrome; AHA, American Heart Association; ESC, European Society of Cardiology; LOE, level of evidence; NSTEMI, non-ST segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

heart rate, while a decrease in nitric oxide caused by increased reactive oxygen species may have led to decreased left ventricular perfusion [41]. Sukumalchantra et al. [39] reported that in ACS patients whose arterial oxygen saturation was over 90%, oxygen administration did not increase oxygen transport to the myocardium because it lowered cardiac output, decreased coronary blood flow, and increased coronary vascular resistance.

Coronary blood flow

In a 1972 study on six subjects with normal coronary arteries and nine subjects with CAD, oxygen therapy was found to reduce coronary sinus blood flow from 158 ± 11 to 131 ± 13 mL/min in the non-CAD and from 151 ± 14 to 138 ± 14 mL/min in the CAD group, presumably due to an increase in coronary resistance [42]. A study by McNulty et al. [43] in 2005, on 18 patients with stable CAD found that relative to room air, breathing 100% oxygen for 15 min increased coronary resistance by approximately 40% and decreased coronary blood flow by approximately 30%.

Mortality

A 2013 systematic review and meta-analysis pooled data from four trials that included 430 participants [44]. The pooled relative risk (RR) of death with oxygen administration was 2.05 (95% CI: 0.75–5.58) in all participants included and 2.11 (95% CI: 0.78–5.68) in participants with confirmed AMI [44]. While suggestive of harm, the study was underpowered to demonstrate a statistically significant increase.

Other adverse events

The Air Versus Oxygen in STEMI (AVOID) trial compared oxygen (8 L/min) with no oxygen in 638 non-hypoxic STEMI patients (defined as O_2sat > 94%). There was a significant increase in mean peak creatinine kinase level in the oxygen group compared with the control group (1948 vs. 1543 U/L; 95% CI: 1.04–1.52; $p = 0.01$) [13]. Furthermore, there was an increase in the rate of recurrent MI in the oxygen group compared with the no oxygen group (5.5% vs. 0.9%, $p = 0.006$) and an increase in cardiac arrhythmia's in normoxic patients who received oxygen (40.4% vs. 31.4%, $p = 0.05$) [13]. There was no statistically significant difference in mortality rates at hospital discharge or in 6-month MACE (defined as all-cause mortality, recurrent myocardial infarction, repeat revascularization, and stroke) [13]. However, the authors acknowledged their study was not powered for clinical endpoints [13]. The 300-patient OXYPAIN trial in 2013 found no reduction in analgesic needs with oxygen therapy [45]. Finally, supplemental oxygen is associated with the development of reactive oxygen species that increase oxidative stress and can directly be arrhythmogenic [46].

Suggestion and future directions

In light of the association between oxygen therapy and recurrent MI, arrhythmias, and infarct size in normoxic patients, we suggest that oxygen therapy should be restricted to hypoxic patients with an O_2 saturation of <90% in both the pre-hospital and in-hospital phases of care. Further randomized controlled trials assessing the benefits and safety of oxygen therapy are warranted. Currently, the DETermination of the role of OXygen in suspected Acute Myocardial Infarction trial (DETO2X-AMI), which is underway in Karolinska, Stockholm, is randomizing 6600 normoxic patients to either supplemental oxygen 6 L/min delivered by oxygen face mask for 6–12 h in the treatment group or room air in the control group, with the end point being 1-year all-cause mortality and will provide more clarity on the benefits or adverse effects of oxygen therapy in normoxic patients (NCT01787110).

Nitrates

Since the 1970s, animal studies and *in vivo* experiments have suggested an advantageous effect for nitroglycerin on

ischemia by reducing ST-elevation and pulmonary capillary wedge pressure [47] (Table 5). However, large RCTs failed to corroborate this benefit.

Guidelines

The latest ESC STEMI guidelines do not recommend the routine use of nitrates in STEMI patients, but state that it is valuable anti-anginal agent in this setting (Table 6) [20]. The 2015 ESC NSTE-ACS guidelines recommend nitrates for the relief of angina, uncontrollable hypertension or heart failure (Class 1, level of evidence C) [21]. However, they state beyond symptom control, there is no indication for nitrate treatment.

The current ACCF/AHA 2013 STEMI guidelines do not provide a formal class recommendation for the use of nitrates in this cohort [22]. The committee state that may be useful to treat patients with STEMI and hypertension or heart failure but they should be avoided in a number of situations including hypotension, marked bradycardia or tachycardia, RV infarction, or 5′phosphodiesterase inhibitor use within the previous 24–48 h [22]. The 2014 ACCF/AHA NSTEMI guidelines provide a Class 1 (level of evidence C) recommendation for sublingual nitrates for patients with continuing ischemic pain up to three doses, after which intravenous nitroglycerin should be considered [23].

Benefits

Coronary blood flow

Nitrates can significantly increase coronary artery blood flow through coronary artery dilation [48].

Antiplatelet effect

Several small mechanistic studies in the late 1980s and early 1990s suggested an anti-platelet effect of nitrates [49]. Nitrates may inhibit platelet activation by activating guanylyl cyclase, increasing cGMP level in platelets leading to a reduction in fibrinogen binding [50]. More recent data in this area are sparse.

Mortality benefit

Three large studies have evaluated the effect of nitrates on mortality in acute MI. The Fourth International Study of Infarct Survival (ISIS-4) examined the use of a slow-release isosorbide mononitrate given for 28 days compared with standard treatment in 58,050 patients [51]. The group found that there was no reduction in mortality at 5 weeks (7.34% vs. 7.54%, $p = 0.3$) or at 1 year among patients allocated to the nitrate compared to placebo [51]. Discontinuation of the study drug due to severe hypotension occurred significantly more frequently with nitrates [51]. The Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico (GISSI-3) trial examined the use of a 24-hour intravenous infusion of glyceryl trinitrate followed by 6 weeks of transdermal glyceryl trinitrate in 19,394 patients and found no significant difference in survival (6.5% compared with the control group 6.9%, $p = 0.28$) [52]. A similar non-significant trend was observed among 4000 patients randomized to the nitric oxide donor molsidomine or placebo in the European study of prevention of infarct with molsidomine (ESPRIM) [53]. After meta-analysis, the combined data from ISIS-4, GISSI-3 and 20 small trials showed a 5.5% mortality reduction with nitrate use ($p = 0.03$), which resulted in 3.8 fewer deaths per 1000 patients treated [54]. However, due to the varied mechanisms by which nitrates were delivered in these trials, these meta-analytic results are difficult to interpret clinically. In summary, while there may be a marginal benefit, the data to date have been inconclusive regarding whether or not nitrates reduce outcomes in acute MI.

Concerns

Right ventricular myocardial infarction

Right ventricular infarction lowers the compliance of the right ventricle, reducing right ventricular filling and stroke volume causing hypotension and on occasion cardiogenic shock. In

Table 5 – The benefits and concerns of nitrates in acute myocardial infarction.

	Form of evidence	Summary	References
Benefits			
Coronary blood flow	Non-randomized controlled trial	Nitrates have a prominent effect on coronary circulation, increasing coronary artery blood flow.	[48]
Anti-platelet effect	Non-randomized controlled trial	Nitrates may inhibit platelet aggregation, which is advantageous in the setting of acute myocardial infarction.	[49,50]
Clinical outcomes	Meta-analysis of randomized controlled trials and observational studies	A meta-analysis of 3 randomized control trials and 20 small studies showed a 5.5% relative risk reduction in mortality with nitrate use ($p = 0.03$), which resulted in 3.8 fewer deaths per 1000 patients treated.	[51–54]
Concerns			
Right ventricular myocardial infarction	Observational study	Nitrates can be detrimental in the setting of right ventricular infarctions where preload is important.	[55]
Hemodynamic effects	Observational studies	Nitrates reduce preload, afterload and can diminish cardiac output leading to hypotension.	[56]
Headache	Observational studies	Headache is the most commonly reported side effect of nitrates in ACS with an incidence of 3–19% in unstable angina and 2–26% in acute myocardial infarction.	[56]

Table 6 – ACCF/AHA and ESC Guidelines for the utility of nitrates in the management of ACS.

	Class of recommendation	LOE
NSTEMI		
AHA/ACCF		
2014	Class 1 recommendation for sublingual nitrates for patients with continuing ischemic pain up to three doses, after which intravenous nitroglycerin should be considered.	C
ECS		
2015	Provide a Class l recommendation for nitrates for the relief of angina, uncontrollable hypertension or heart failure in NSTEMI patients.	C
STEMI		
AHA/ACCF		
2013	No formal recommendation provided. However, the committee advise that nitrates may be useful to treat patients with STEMI and hypertension or heart failure but they should be avoided in a number of situations including hypotension, marked bradycardia, or tachycardia, RV infarction, or 5′phosphodiesterase inhibitor use within the previous 24–48 h.	
ESC		
2012	No formal recommendation given. However, the committee advise that nitrates are a valuable anti-anginal agent in this setting.	

ACCF, American College of Cardiology Foundation; ACS, acute coronary syndrome; AHA, American Heart Association; ESC, European Society of Cardiology; LOE, level of evidence; NSTEMI, non-ST segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

such cases, nitrates that reduce preload, can diminish cardiac output and induce significant hypotension [55].

Hemodynamic effects

Nitrates reduce preload, afterload, and can diminish cardiac output leading to hypotension [56]. Thus, they should not be given to patients with hypotension, marked bradycardia, or tachycardia, or in patients with 5′phosphodiesterase inhibitor use within the previous 24–48 h.

Headache

Headache is the most commonly reported side effect of nitrates in ACS with an incidence of 3–19% in unstable angina and 2–26% in acute myocardial infarction [56].

Suggestions and future directions

While there has been some signal of benefit, there is no definitive evidence demonstrating that nitrates improve outcomes in ACS. Thus in keeping with guideline recommendations, their utility in ACS is based on symptom control and individualized to clinical presentation. They should be avoided in patients with hypotension and in patients with a right ventricular infarction.

Conclusion

Morphine, oxygen, and nitrates are traditionally recommended when formulating the initial management plan for ACS patients. However, these agents are supported by very limited evidence. Even more concerning, recent studies have suggested that two of these medications—morphine and oxygen—may be associated with adverse outcomes in certain ACS populations [2,3]. Arguably, these therapies are an example of an increasingly recognized phenomenon, where long-standing and historically established therapies are often found to be lacking when subjected to randomized trials [57,58]. Further randomized control trials to establish to establish the benefits and safety of these agents are now needed and are already underway. Moreover, state-of-the-art quasi-experimental statistical techniques to help answer comparative effectiveness questions using increasingly available large databases would be of major additional utility [59].

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