Effect and Safety of Morphine Use in Acute Anterior ST-Segment Elevation Myocardial Infarction

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***Background*—**Morphine is commonly used to treat chest pain during myocardial infarction, but its effect on cardiovascular outcome has never been directly evaluated. The aim of this study was to examine the effect and safety of morphine in patients with acute anterior ST-segment elevation myocardial infarction followed up for 1 year.

***Methods and Results*—**We used the database of the CIRCUS (Does Cyclosporine Improve Outcome in ST Elevation Myocardial Infarction Patients) trial, which included 969 patients with anterior ST-segment elevation myocardial infarction, admitted for primary percutaneous coronary intervention. Two groups were defined according to use of morphine preceding coronary angiography. The composite primary outcome was the combined incidence of major adverse cardiovascular events, including cardiovascular death, heart failure, cardiogenic shock, myocardial infarction, unstable angina, and stroke during 1 year. A total of 554 (57.1%) patients received morphine at first medical contact. Both groups, with and without morphine treatment, were comparable with respect to demographic and periprocedural characteristics. There was no significant difference in major adverse cardiovascular events between patients who received morphine compared with those who did not (26.2% versus 22.0%, respectively; P=0.15). The all-cause mortality was 5.3% in the morphine group versus 5.8% in the no-morphine group (P=0.89). There was no difference between groups in infarct size as assessed by the creatine kinase peak after primary percutaneous coronary intervention (4023±118 versus 3903±149 IU/L; P=0.52).

***Conclusions*—**In anterior ST-segment elevation myocardial infarction patients treated by primary percutaneous coronary intervention, morphine was used in half of patients during initial management and was not associated with a significant increase in major adverse cardiovascular events at 1 year.

Key Words: clinical • morphine • opioid • percutaneous coronary intervention • pharmaceutical safety • ST-segment elevation myocardial infarction

Morphine is currently used and recommended for the treatment of chest pain during myocardial infarction, but the level of evidence is low, attributed to the lack of supportive clinical studies.[1–4]

Moreover, the American Heart Association has relegated morphine use in patients with non-ST-segment elevation myocardial infarction from a Class I to a Class IIa recommendation.[3] This modification was driven by the results from the

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Clinical Perspective

What Is New?

- This retrospective study evaluating outcomes associated with morphine use in an ST-segment elevation myocardial infarction population provides additional data that use of morphine is not associated with adverse outcomes.

What Are the Clinical Implications?

- Use of morphine to relieve chest pain is safe in patients with ST-segment elevation myocardial infarction.

CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the American College of Cardiology/American Heart Association Guidelines) registry showing that, in patients with non-ST-segment elevation myocardial infarction, morphine use increased the risk of death and adverse outcome.[5] Morphine has also been associated with suboptimal reperfusion success and a low myocardial salvage index after primary percutaneous coronary intervention (PPCI) in patients presenting with ST-segment elevation myocardial infarction (STEMI).[6]

Nevertheless, in 2 independent cohorts from the FAST-MI (French Registry of Acute ST-elevation and non-ST-elevation Myocardial Infarction) registry, prehospital morphine use in STEMI patients did not increase in-hospital complications or 1-year mortality.[7] Because of this controversy, additional investigations are necessary.

The aim of this study was to explore the effect of morphine on clinical outcomes in a population of patients with anterior STEMI referred for PPCI.

Methods

The data, analytical methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Design

We used the database of the recently published CIRCUS (Does Cyclosporine Improve Outcome in ST Elevation Myocardial Infarction Patients) trial[8,9] for a post hoc analysis assessing the effect of morphine use in the initial management of patients with anterior STEMI undergoing PPCI.

CIRCUS was an international, multicenter, double-blind, placebo-controlled trial conducted between April 2011 and February 2014. The CIRCUS trial showed no significant effect of cyclosporine on the clinical outcomes of patients with anterior STEMI.[9]

CIRCUS study was performed in accord with the principles of the Declaration of Helsinki and the European guidelines for Good Clinical Practice. Approval was obtained from the ethics committees in the relevant countries, and written consent for data use was obtained from all patients.

Study Population

We analyzed data from the intent-to-treat population of the CIRCUS trial.

Eligible patients (male and female) were aged ≥18 years and presented within 12 hours of onset of symptoms evocative of acute coronary syndrome (ACS). They were required to have ST-segment elevation ≥0.2 mV in 2 anterior contiguous leads and to be scheduled for PPCI. Written informed consent was obtained from all patients.

Exclusion criteria included cardiogenic shock or loss of consciousness during the prehospital period, known hypersensitivity to cyclosporine, known kidney or liver failure, pregnancy or absence of contraception in women of childbearing age, and any disorder associated with immunological dysfunction within the previous 6 months.

Study Treatment

CIRCUS patients were divided into 2 groups with and without intravenous morphine before PPCI. In a post-hoc analysis setting, we hypothesized that morphine use would be superior to the absence of morphine use in terms of primary outcomes.

Study Outcomes

The primary outcome was the rate of occurrence of major adverse cardiovascular event (MACE) including cardiovascular death, heart failure, cardiogenic shock, recurrent myocardial infarction, unstable angina, and stroke during 1 year of follow-up. Cardiogenic shock was defined as systolic blood pressure <80 mm Hg for >30 minutes, unresponsive to fluid replacement, and associated with signs of peripheral and end-organ hypoperfusion. Heart failure was defined as clinical symptoms requiring initiation or intensification of heart failure treatment with intravenous administration of diuretics. Unstable angina was defined as the presence of acute chest pain associated with ST depression, or new onset of negative T waves, and no elevation of troponins.

Secondary outcomes included rate of occurrence of individual MACE, all-cause death, adverse left ventricular remodeling during 1 year of follow-up, and the creatine phosphokinase (CPK) peak blood concentration in the 24 hours post-PPCI.

MACE were adjudicated by an event validation committee composed of at least 3 cardiologists/physicians blinded to

treatment. Total CPK blood concentration was measured in peripheral total blood at the time of PPCI and 4, 12, and 24 hours post-PPCI. CPK measures were conducted locally, in each participating center. CPK peak concentration was defined as the highest value collected during the 24 hours post-PPCI. It was used as an indirect evaluation of infarct size.[10,11] Adverse left ventricular remodeling was defined as an increase of 15% or more of end diastolic left ventricular volume indexed to body surface area. End diastolic volume was measured at discharge and at 1 year by blinded expert readers. The measures were performed on echocardiographic data, according to the Simpson biplane rule.

Subgroup Analysis

Cyclosporine is an inhibitor of cerebral[12] and intestinal[13] P-glycoprotein. P-glycoproteins are involved in morphine intestinal absorption[14] and neurological circulation.[15] This P-glycoprotein inhibition could lead to an increased effect of morphine.[14]

To evaluate the effect of this pharmacological interaction on our results, we compared the 4 subgroups: morphine with cyclosporine; morphine with placebo; no morphine with cyclosporine; and no morphine with placebo on MACE occurrence and on infarct size. We also explored morphine with cyclosporine interaction effect on MACE occurrence by 2-way ANOVA with an interaction term.

Statistical Analysis

All statistical analyses were post hoc and were not prespecified in the original CIRCUS Statistical Analysis Plan.

Continuous variables with normal distribution are expressed as means and SDs. Continuous variables with a non-normal distribution are expressed as medians and interquartile ranges. Normality was tested with the Shapiro–Wilk test. Categorical variables are expressed as percentages. The study population was divided into 2 groups according to morphine use. Comparison of baseline characteristics or outcomes was performed using the chi-squared test or Fischer's exact test, as appropriate, for categorical variables. The Student *t* test was used for continuous variables with normal distribution and the Wilkoxon test for continuous variables with non-normal distribution. Unadjusted event-free survival was evaluated by Kaplan–Meier estimates, and comparison between groups was conducted using the log-rank test. Adjusted risk estimates were obtained using the Cox proportional hazards model, including variables found to differ significantly between groups on univariate analysis or deemed to be clinically relevant.

For all comparisons, a value of $P<0.05$ was considered statistically significant. When appropriate, 95% confidence intervals were calculated.

All statistical analyses were conducted using STATA software (version SE 14.2; (StataCorp LP, College Station, TX).

Results

The intent-to-treat CIRCUS population included 969 patients.[8,9] Two patients were not included in our analysis because of lack of information on morphine use. Morphine was used before PPCI in 554 (57.3%) patients. Baseline characteristics (Table 1) and periprocedural characteristics (Table 2) were well balanced between groups with and without morphine use. There was a nonsignificant trend toward younger age and a shorter total ischemic time in patients receiving morphine. There was also a trend toward more heart failure and cardiogenic shock in the morphine group: 13.1% versus 10.2% of patients admitted in Killip 2 or 3 and 1.4% versus 0% of patients admitted with cardiogenic in morphine and no-morphine group, respectively (Table 2).

At 1 year, 236 (24.4%) patients had experienced at least 1 MACE. There was no significant difference in occurrence of MACE between groups: 145 (26.2%) and 91 (22.0%) patients in the groups with and without morphine, respectively ($P=0.15$; Table 3). Cumulative Kaplan–Meier estimates for the first occurrence of MACE (Figure 1) were not significantly different between groups ($P=0.10$).

In the Cox model, morphine use was not associated with the incidence of MACE (hazard ratio=1.25; 95% confidence interval [0.96; 1.62]; $P=0.10$), even after adjustment for age, ischemic time, infarct size (CPK peak), initial and final Thrombolysis in Myocardial Infarction flow, sex, smoking, hypertension, diabetes mellitus, previous myocardial infarction, and Killip class (hazard ratio=1.04; 95% confidence interval [0.75; 1.45]; $P=0.82$).

Incidence of individual MACE during 1 year was not significantly different between groups (Table 3; Figure 2).

There was no statistically significant difference on MACE occurrence ($P=0.56$) and on infarct size ($P=0.61$) between the 4 different treatment subgroups (Table 4). Interaction term, even after adjustment, was not significant and so for each clinical outcome individually (Table S1).

There was no significant difference in rates of all-cause death at 1 year between groups (32 [5.3%] and 22 [5.8%] deaths in the groups with and without morphine, respectively; $P=0.89$).

The unadjusted Kaplan–Meier hazard curve for 1-year all-cause mortality is presented in Figure 3. No significant difference was observed between the groups with and without morphine ($P=0.77$).

CPK peak blood concentrations after PPCI were comparable in both groups (4023 ± 118 and 3903 ± 149 IU/L in the groups with and without morphine, respectively; $P=0.52$; Figure 4).

Table 1. Characteristics of the Patients at Baseline

	All Patients (n=967)	Patients With Morphine (n=554)	Patients Without Morphine (n=413)	*P* Value (Wilcoxon or Fisher's Test)
Age, y	60±13	59±13	61±13	0.07
Male sex, %	82	82	82	0.73
Body mass index, kg/m^2	27±4	27±4	27±4	0.14
Current smoker, %	42	43	41	0.39
Hypertension, %	37	38	37	0.74
Diabetes mellitus, %	13	13	13	1.00
Dyslipidemia, %	38	40	36	0.18
Previous myocardial infarction, %	6	6	5	0.67
Previous PCI, %	7	7	6	0.61
LVEF, %	47±10	47±10	48±10	0.16
Cyclosporine use before PPCI, %	49	51	46	0.12

Values are expressed as means±SD. LVEF indicates left ventricular ejection fraction (measured by echocardiography); PCI, percutaneous coronary intervention; PPCI, primary percutaneous coronary intervention.

Rates of adverse left ventricular remodeling were also similar in both groups (205 [37.0%] and 134 [32.4%] patients with adverse remodeling in the groups with and without morphine, respectively; *P*=0.21).

Discussion

In a large cohort of patients with acute anterior STEMI, morphine was used in half of patients before PPCI and had no significant effect on the composite primary outcome including cardiovascular death, heart failure, cardiogenic shock, recurrent myocardial infarction, unstable angina, and stroke.

Few other studies have evaluated the clinical outcomes of patients who received morphine to alleviate chest pain during an ACS.[16] In line with our results, 2 retrospective studies concluded that morphine/intravenous narcotics did not adversely affect the outcomes in patients with ACS. In 1 study including 1758 patients (765 STEMI and 993 non-ST-segment elevation myocardial infarction), the rate of 30-day death was not increased with the use of intravenous narcotics.[17] In the second study, the analysis of 2 cohorts of STEMI patients (2438 patients from the FAST-MI 2010 registry and 1726 from the FAST-MI 2005)[7] suggested that prehospital morphine use was not associated with increased in-hospital complications and 1-year mortality.

On the contrary, an American retrospective study based on the CRUSADE registry,[5] which included 57 039 patients who presented with non-ST-segment elevation ACS, reported an increase in mortality and challenged the safety of morphine use in these patients. It is difficult to compare the CRUSADE study with ours because of differences in population, study dates, and design. The CRUSADE study retrospectively enrolled non-ST-segment elevation ACS patients, who are different from STEMI patients. It was conducted between 2002 and 2003, at a time when oral antiplatelet agent use was limited to clopidogrel, which has more pharmacological interactions with morphine than more recently approved agents such as ticagrelor and prasugrel.[18,19]

Thus, it seems that there is currently limited evidence for adverse outcomes associated with morphine use in STEMI patients, whereas additional caution may be necessary in NSTEMI patients.

In our study, morphine use did not appear to be associated with any significant cardioprotective effect. Myocardial protection with opioid use has been inconsistently reported. Several studies suggest a cardioprotective effect especially with morphine in the surgical context of coronary artery bypass graft, but these studies were conducted in small surgical patient populations and assessed indirect outcomes.[20,21] In STEMI patients undergoing PPCI, a cardioprotective effect could be demonstrated for morphine in addition to the basal effect of remote ischemic conditioning,[22] but no additional myocardial protection was observed with fentanyl in patients undergoing elective PPCI.[23]

In experimental models of ischemia reperfusion injury, morphine inhibits the mitochondrial permeability transition pore[24] opening through μ and κ myocardial opioid receptors,[25,26] and induced a significant cardioprotective effect.[27] Morphine also stimulates the reperfusion injury salvage kinase pathway.[24] In animal studies, these mechanisms have been associated with a reduction of infarct size following intravenous or intrathecal morphine use before or immediately after reperfusion.[28–30] However, the translation from animal models to humans is not straightforward owing to disease complexity and associated

Table 2. Periprocedural Characteristics

	Patients With Morphine (n=554)	Patients Without Morphine (n=413)
Killip class at admission	505	353
Class 1	432 (85.5)	317 (90.0)
Class 2	57 (11.3)	29 (8.2)
Class 3	9 (1.8)	7 (2.0)
Class 4	7 (1.4)	0 (0.0)
Total ischemic time, mean±SD (h)	3.99±2.39	4.94±3.07
Rentrop Grade 2 or 3	34/554 (6.1)	31/413 (7.5)
Angiographic thrombus burden ≥3	358/533 (67.2)	267/395 (67.9)
Area at risk, mean±SD (%)*	36.8±8.4	35.6±8.6
Proximal localization	252/552 (45.6)	157/403 (38.9)
Multivessel disease	203/554 (36.6)	154/413 (37.3)
Thrombolysis rate	33/554 (5.9)	27/413 (6.5)
Stenting	492/554 (88.8)	362/413 (87.6)
No reflow	30/554 (5.4)	25/413 (6.1)
Final TIMI	548	403
TIMI=0	9 (1.6)	4 (1.0)
TIMI=1	2 (0.3)	8 (2.0)
TIMI=2	29 (5.3)	29 (7.2)
TIMI=3	508 (92.7)	362 (89.8)
Treatment at discharge		
Double antiplatelet treatment	511/544 (93.9)	380/408 (93.1)
Beta-blockers	507/544 (93.2)	370/408 (90.7)
Statins	522/544 (95.9)	389/408 (95.3)
ACEi	482/544 (88.6)	348/408 (85.3)
ARB	10/544 (1.8)	15/408 (3.7)
Calcium-channel blockers	12/544 (2.2)	13/408 (3.2)
Diuretics	138/554 (25.4)	105/413 (25.4)
Aldosterone antagonists	147/544 (27.0)	82/408 (20.1)

Values are expressed as numbers (percentages), unless otherwise specified. ACEi indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; TIMI, Thrombolysis in Myocardial Infarction.
*Using the APPROACH angiographic score.

comorbidities, and our data do not suggest any cardioprotective effect of morphine on ischemia-reperfusion injury. In the near future, 2 noncurrently published studies (Clinical Trials NCT01186445 and NCT01738100) may provide additional understanding of the cardioprotective effects of intracoronary morphine during ACS.

In recent years, there has been a growing concern about the use of morphine for pain relief in patients with ACS.

Table 3. Clinical Outcome After 1-Year Follow-up

Event	Morphine (n=554)	No Morphine (n=413)	*P* (Fischer's Test)
Any MACE*	145 (26.2)	91 (22.0)	0.15
Cardiovascular death	29 (5.2)	20 (4.8)	0.88
Heart failure	110 (19.9)	70 (16.9)	0.28
Cardiogenic shock	30 (5.4)	19 (4.6)	0.66
Recurrent myocardial infarction	21 (3.8)	7 (1.7)	0.08
Unstable angina	15 (2.7)	8 (1.9)	0.53
Stroke	10 (1.8)	9 (2.2)	0.82

Values are expressed as numbers (percentages). MACE indicates major adverse cardiovascular events.
*A patient with more than 1 clinical event was counted as having 1 MACE.

Morphine delays and attenuates the release peak and efficacy of oral antiplatelet agents in ACS[31–33] and healthy[18,19,34] patients, by inhibiting gastrointestinal absorption[35] and inducing to vomiting.[16] However, there is no evidence for the clinical relevance of these effects. In our study, although morphine was not associated with any adverse outcome in STEMI patients, there was a nonsignificant trend toward an increase in individual MACE in patients treated with morphine. In particular, recurrent myocardial infarction and heart failure seemed to be more frequent when morphine was used before PPCI, although these results did not reach statistical significance (*P*=0.08 and 0.28, respectively; Table 3).

Regardless of the potential outcome modifications associated with morphine use during ACS, pain release is essential to decrease patients' discomfort and to avoid proarrhythmic anxiety. In our study, 42.7% patients did not receive any analgesia, meaning that pain was probably undertreated. This is not acceptable, and pain release should be a priority of any medical care. Without ethical possibility of a placebo-controlled, randomized study, it is difficult to conclude

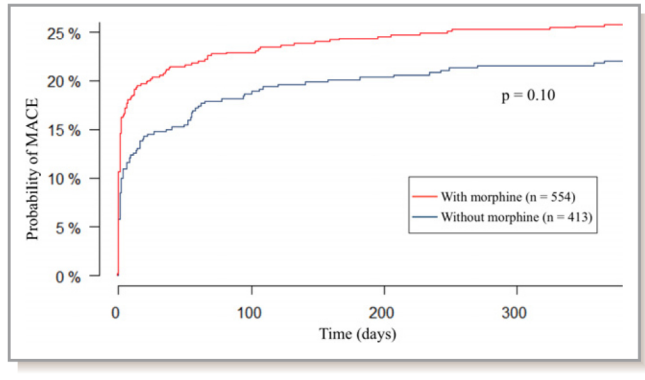

Figure 1. Kaplan–Meier curves for major adverse cardiovascular events (MACE).

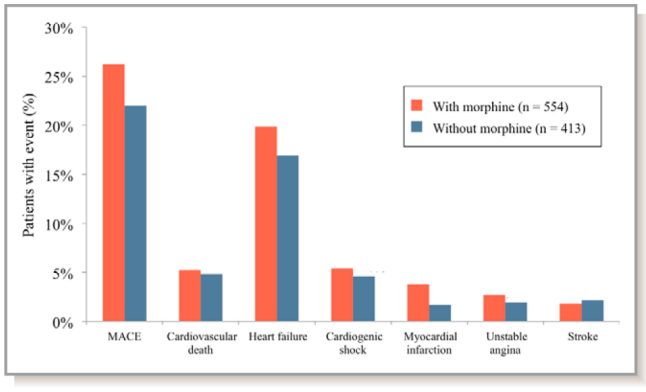

Figure 2. Occurrence of major adverse cardiovascular events (MACE) and individual events after 1-year of follow-up.

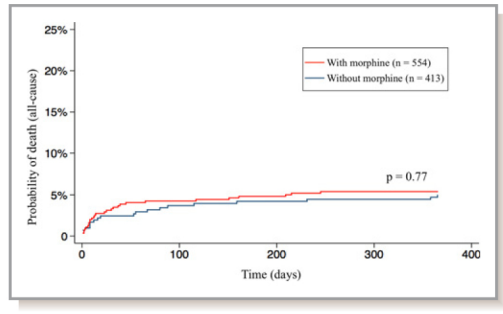

Figure 3. Kaplan–Meier curves for 1-year all-cause mortality.

definitively about morphine safety in this indication. There is no analgesic alternatives to morphine in this indication, and the only new approach currently evaluated is equimolar oxygen/nitrous oxide mixture (MEOPA) associated with paracetamol, under investigation in the ongoing SCADOLII (Comparison of MEOPA + Paracetamol Versus Morphine Treatment in Acute Coronary Syndrome Analgesia) trial. In the absence of clear evidence of adverse effects, morphine should be used without restraint in STEMI as was concluded in a recent review.[16]

Study Limitations

Although analyses were conducted on a prospective homogenous anterior STEMI population, they were post hoc analyses, not prespecified in the original CIRCUS protocol, leading to a loss of statistical relevance and limited statistical power.

Given that CIRCUS trial randomization was not stratified on morphine use, the effect of unmeasured confounders on the results cannot be ruled out. Anyway, patients in the morphine group seemed to be sicker at initial medical care than those in the no-morphine group: 13.1% of patients were admitted with heart failure (Killip 2 or 3) in the morphine group versus 10.2% in the no-morphine group; 1.4% of patients were admitted with cardiogenic shock in the morphine group versus 0% in the no-morphine group. There was no randomization, nor precise recommendation, for morphine use in the CIRCUS protocol. So, morphine could have been used as a symptomatic treatment, in combination with continuous positive airway pressure, for patients suffering from dyspnea or acute heart failure at first medical care. Initial heart failure and/or cardiogenic shock are strongly associated with a poorest prognosis.[36] Despite this initial difference, the morphine group did not experience significantly more adverse events than the no-morphine group.

The study was not initially designed to evaluate the effect of morphine in patients with anterior STEMI, so the investigation was limited by the number of subjects. It is difficult to evaluate precisely the statistical power of our work. For example, if we previously calculated the number needed to treat with the hypothesis of the 4.2% absolute difference between groups observed in our study, with 80% power and 5% alpha risk, triple sample size would have been necessary. So, limited sample sizes may explain the lack of statistical significance of the observed difference in our work.

The use of cyclosporine, even though its known interactions with morphine intestinal absorption and neurological effect, had no significant effect on the results of our study. There was no statistically significant difference between the 4 different subgroups defined by the use of cyclosporine and of morphine, nor significant interaction between morphine and cyclosporine.

In the morphine group, we did not record the dose of morphine that was administered as well as corresponding pain scales. Further studies are needed to assess precisely pain management in STEMI patients and its potential impact on clinical outcomes

Table 4. Subgroups Analysis, Evaluation of Morphine—Cyclosporine Interactions

	Morphine+Cyclosporine (n=266)	Morphine+Placebo (n=246)	No Morphine+Cyclosporine (n=178)	No Morphine+Placebo (n=205)	*P* (ANOVA)
MACEs*	70 (26.3)	75 (30.5)	44 (24.7)	47 (22.9)	0.56
CPK peak†	3945±2638	4054±2677	4061±3182	3742±2571	0.61

CPK indicates creatine phosphokinase; MACE, major adverse cardiovascular events.
*Values are expressed as numbers (percent).
†Values are expressed as mean±SD.

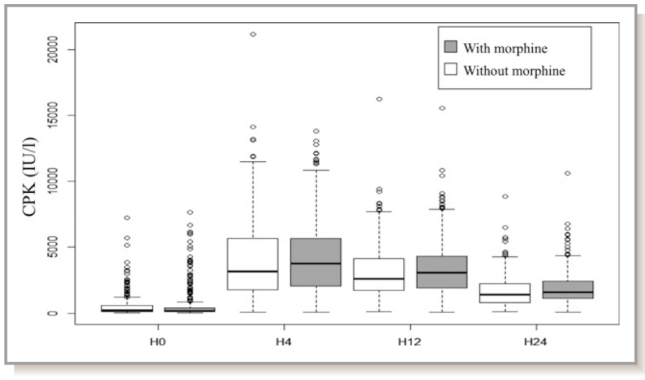

Figure 4. Creatine phosphokinase (CPK) blood concentration evolution during the first 24 hours following primary percutaneous coronary intervention (PPCI)—median, first and third quartiles, and first and ninth decile are presented for each measurement. Mixed-model analysis for morphine effect on CPK kinetic curve: *P*=0.09.

Conclusion

In the prospective CIRCUS trial, intravenous morphine was used in half of patients and was not associated with any significant modification in MACE occurrence at 1 year. Further large, randomized studies are needed to assess the impact of morphine use on clinical outcomes and pain management strategies in STEMI patients.

Appendix

Contributors

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Disclosures

None.

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Table S1. Interaction of morphine with cyclosporine effect on MACE occurrence, explored by two ways ANOVA with interaction term.

	Odds ratio [95% CI]	P value
MACE	0.75 [0.41-1.38]	0.36
Adjusted MACE*	1.09 (0.56-2.11)	0.79
Cardiovascular death	1.53 [0.47-5.14]	0.48
Recurrent myocardial infarction	0.29 [0.05-1.71]	0.17
Heart failure	0.55 [0.28-1.07]	0.08
Unstable angina	0.7 [0.12-4.11]	0.69
Cardiogenic shock	0.57 [0.17-1.87]	0.36
Stroke†	15.82 [1.76-375.51]	0.03
All cause death	1.92 [0.62-6.21]	0.26

* Adjusted for age, ischemic time, infarct size (CPK peak), initial and final TIMI flow, sex, smoking, hypertension, diabetes, previous MI and Killip Class.

† Interaction term was significant ($p < 0.05$), but individually the other terms of the interaction were not significant: morphine $p = 0.08$ (OR [95%IC]: 0.3 [0.07-1.06]) and cyclosporine $p = 0.07$ (0.14 [0.01-0.79]). Indeed, for stroke, interaction was not interpretable.