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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

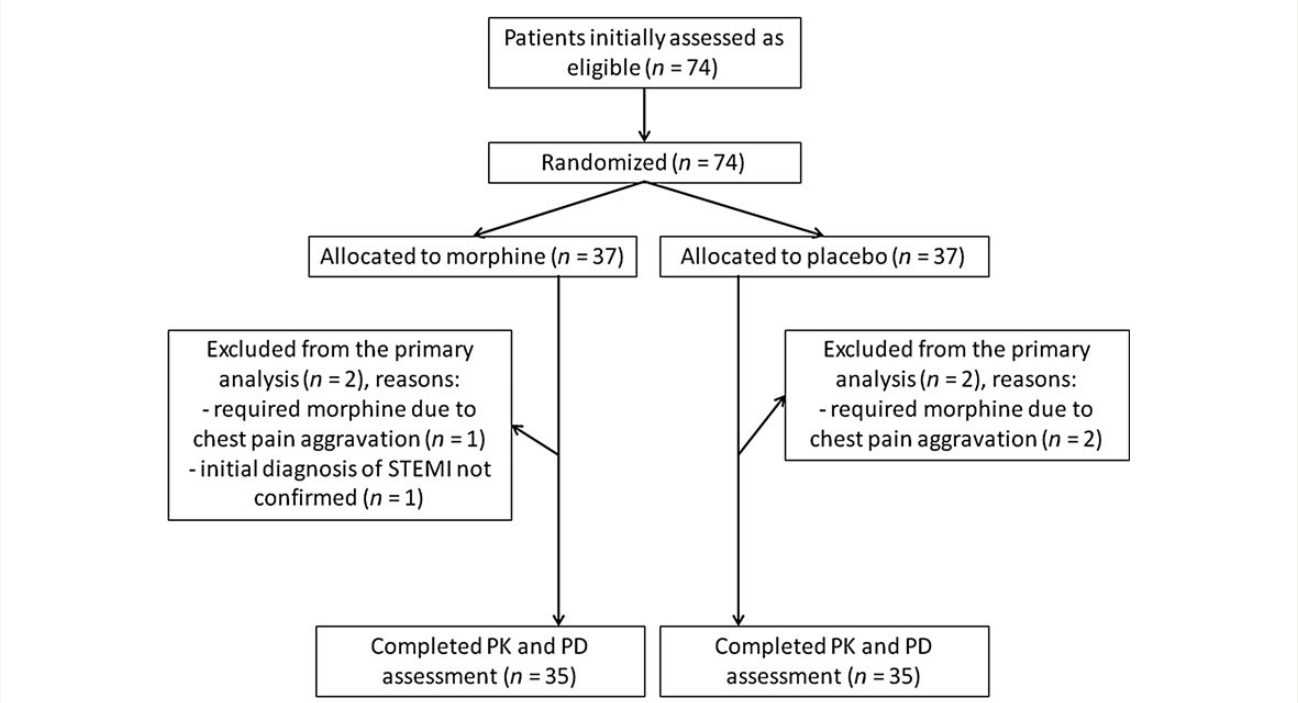

Figure 1 Patient flow diagram. PD, pharmacodynamic; PK, pharmacokinetic; STEMI, ST-elevation myocardial infarction.

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

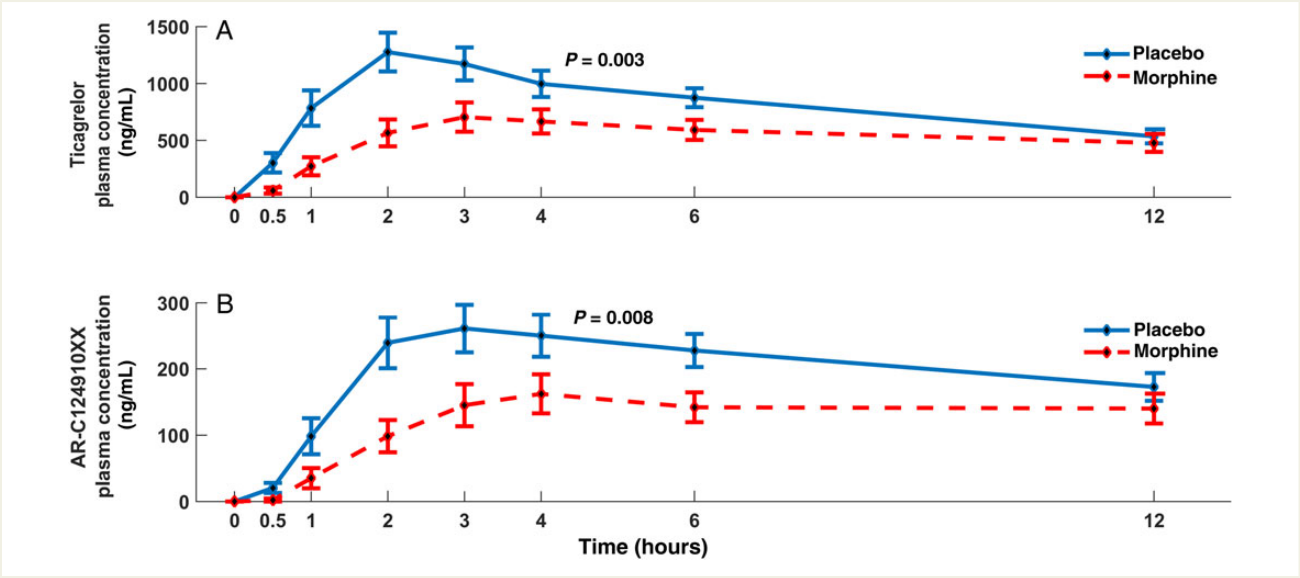

Figure 2 Plasma concentrations of ticagrelor and AR-C124910XX. Plasma concentrations of (*A*) ticagrelor and (*B*) AR-C124910XX after oral administration of a 180 mg ticagrelor loading dose, which followed intravenous injection of placebo (blue) or morphine (red).

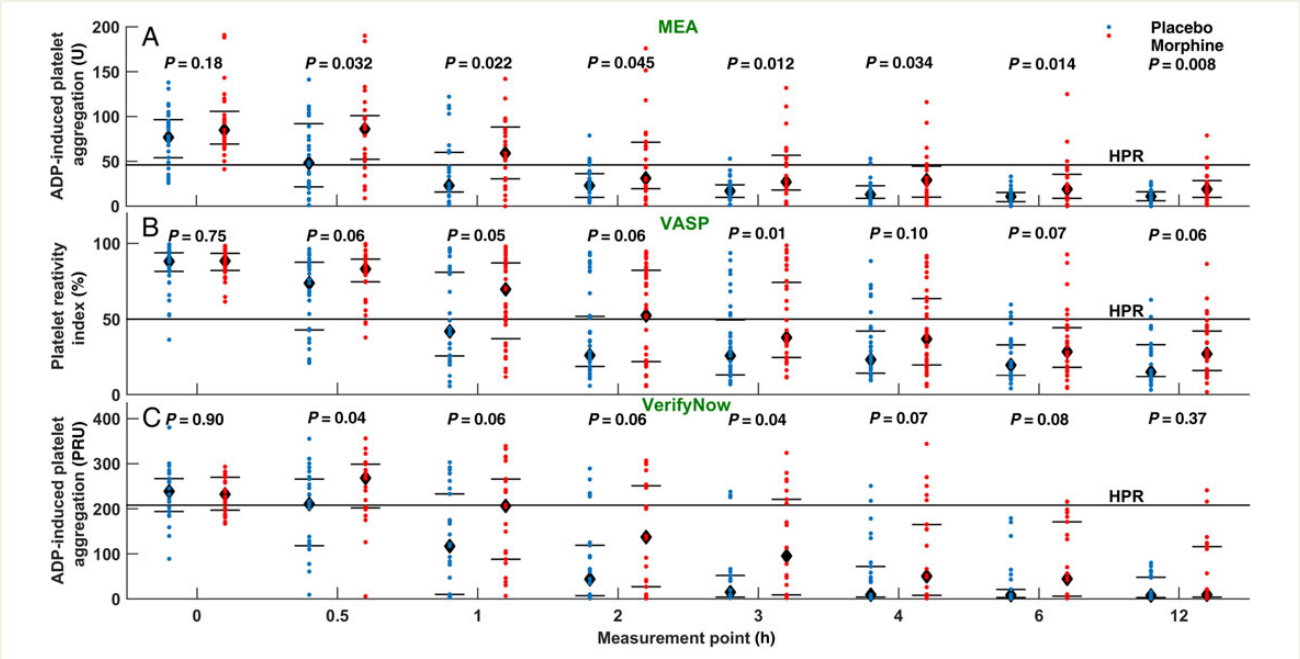

Figure 3 Platelet reactivity over time in morphine vs. placebo-treated patients. Platelet reactivity assessed with (*A*) MEA ($n = 54$), (*B*) VASP ($n = 70$), and (*C*) VerifyNow P2Y12 ($n = 48$) tests at baseline, and at 30 min, 1, 2, 3, 4, 6, and 12 h after administration of a 180 mg ticagrelor loading 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; $P = 0.33$].

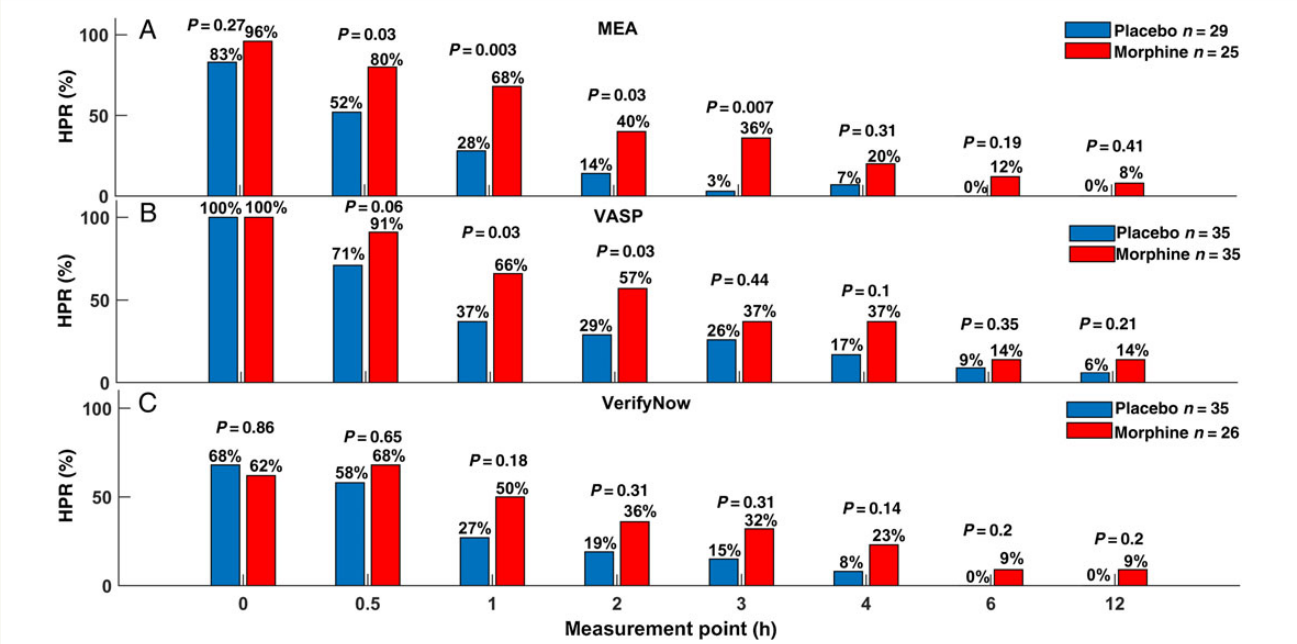

Figure 4 Prevalence of high platelet reactivity over time in morphine vs. placebo-treated patients. Proportion of patients with high platelet reactivity assessed with (*A*) MEA, (*B*) VASP, and (*C*) VerifyNow P2Y12 tests at pre-defined measurement points in relation to administration of morphine (red)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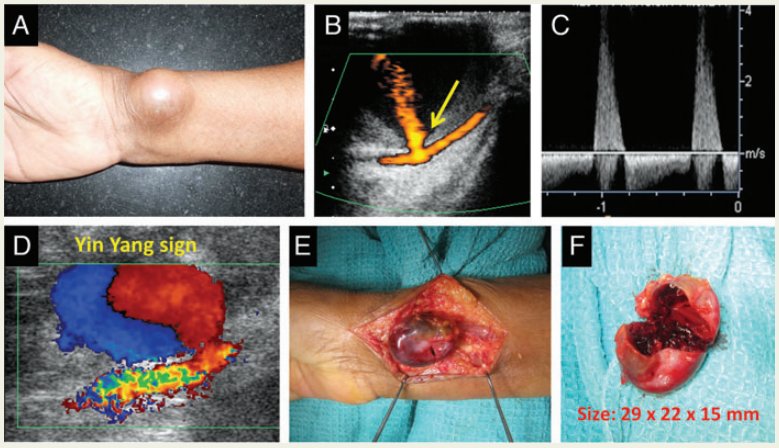

A 54-year-old lady presented with Canadian cardiovascular society class II stable angina of 6 months duration. Clinical examination and investigations were unremarkable, including normal echocardiogram. She underwent elective coronary angiogram through right radial access, which revealed double vessel 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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