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Oral NAloxone to overcome the moRphine effect in acute COronary syndrome patients treated with TICagrelor — NARCOTIC trial

Running title: NARCOTIC Trial

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Abstract

Background: Numerous worldwide clinical trials have proven the indisputably negative influence of morphine on the pharmacokinetics and pharmacodynamics of P2Y₁₂ receptor inhibitors in patients presenting with acute coronary syndromes. The aim of this trial was to evaluate whether oral co-administration of an anti-opioid agent, naloxone, can be considered a successful approach to overcome ‘the morphine effect’.

Methods: Consecutive unstable angina patients receiving ticagrelor and morphine with or without orally administered naloxone underwent assessment of platelet reactivity using Multiplate analyzer as well as evaluation of the pharmacokinetic profile of ticagrelor and its active metabolite, AR-C124910XX, at nine pre-defined time points within the first 6 hours following oral intake of the ticagrelor loading dose.

Results: The trial shows no significant differences regarding the pharmacokinetics of ticagrelor between both study arms throughout the study period. AR-C124910XX plasma concentration was significantly higher 120 min after the ticagrelor loading dose administration ($p = 0.0417$). However, the evaluation of pharmacodynamics did not show any statistically significant differences between the study arms.

Conclusions: To conclude, this trial shows that naloxone co-administration in ticagrelor-treated acute coronary syndrome patients on concomitant treatment with morphine shows no definite superiority in terms of ticagrelor pharmacokinetic and pharmacodynamic profile.

Key words: acute coronary syndrome, unstable angina, ticagrelor, morphine, naloxone

Introduction

The development of contemporary treatment of acute coronary syndromes (ACS) has forced the establishment of methods of rapid platelet inhibition. The results of the PLATO trial proved the superiority of ticagrelor over well-known and widely used clopidogrel in terms of its effectiveness, mainly demonstrated by the reduction of the composite endpoint including cardiovascular death, myocardial infarction or stroke with no significant increase of the risk of clinically significant bleeding [1]. Based on those findings ticagrelor has become the treatment of choice in patients presenting with ACS according to currently available guidelines [2–6].

Numerous ACS patients, especially those presenting with ST-segment elevation myocardial infarction (STEMI), require strong and effective analgesia. The most commonly used analgesic medication nowadays is morphine [2]. Morphine administration used to be considered beneficial for ACS patients as it was thought to be associated not only with pain alleviation, but also with a positive tranquilizing effect on treated individuals. Several international studies however, have revealed a negative interaction between morphine and P2Y₁₂ receptor inhibitors leading to decrease of the plasma concentrations of those platelet inhibitors and their metabolites as well as delay and attenuation of their antiplatelet activity. [7–11]. The discovery of the negative influence of morphine on the PK/PD profile of

ticagrelor in ACS patients resulted in a decrease of class of recommendation for morphine use to class IIa for STEMI based on the latest guidelines [2]. Morphine has been found to negatively influence gastric emptying, impair intestinal motility, reduce intestinal secretion and induce nausea or vomiting [12]. The phenomenon presented above can be called ‘the morphine effect’.

Naloxone, a selective opioid receptor antagonist, is widely used to diminish negative effects of opioid drugs. Its utility is most pronounced in opioid substitution therapy in cases of opioid addiction or reversal of opioid action in opioid intoxication. Typically, in such clinical situations, naloxone is administered parenterally. However, if administered orally, it has been proven to successfully reduce the negative impact on gastrointestinal tract by relieving opioid-related constipation in oncological patients requiring regular opioid administration. This approach allows the elimination of intestinal motility impairment without risking attenuation of the analgesic activity of an opioid, as naloxone administered orally is associated with a strong first-pass effect making its serum concentration barely detectable. The final bioavailability of the drug after oral administration ranges from 2% to 3% [13–16].

On the basis of the aforementioned findings it was hypothesized that co-administration of naloxone may prove beneficial as a potential method of overcoming ‘the morphine effect’ in ACS patients treated with ticagrelor who received morphine.

Methods

Study design and population

A pharmacokinetic/pharmacodynamic, phase IV, single center, investigator-initiated, randomized, open-label, active-controlled trial was designed and it was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki guidelines. The previously published study protocol [17] was approved by The Ethics Committee of The Nicolaus Copernicus University in Torun, Collegium Medicum in Bydgoszcz (approval number KB 540/2015). Any study-related procedures were undertaken only after obtainment of informed consent to participate in the trial from each study participant. Males and non-pregnant females, aged 18–80 years, admitted to the Department of Cardiology, A. Jurasz University Hospital in Bydgoszcz, Poland due to unstable angina and qualified for coronary angiography, underwent eligibility screening. The complete list of inclusion and exclusion criteria is presented in Figure 1.

Patients admitted to the Department of Cardiology, due to unstable angina received orally a 300 mg loading dose (LD) of plain acetylsalicylic acid (Polpharma SA, Starogard

Gdansk, Poland) and underwent eligibility screening for participation in the study. Having consented to participate in the trial, eligible patients were randomized in a 1:1 ratio into two study arms as follows — the active study arm including patients receiving: 1) crushed tablets of 180 mg ticagrelor in 10 mL suspension in tap water administered orally; 2) 5 mg of morphine administered intravenously; 3) 1 mg of naloxone administered orally; and the control group treated with: 1) crushed tablets of 180 mg ticagrelor in 10 mL suspension in tap water administered orally; and 2) 5 mg of morphine administered intravenously. The Random Allocation Software version 1.0. was used for the process of randomization.

Based on the results of studies previously conducted in the present department, oral administration of crushed ticagrelor was chosen as it was associated with the optimal pharmacokinetic and pharmacodynamic profile in unstable angina patients [18]. Only patients with low and intermediate risk of in-hospital mortality as assessed with the GRACE scale were enrolled in the study, which allowed completion of the whole blood sampling schedule before coronary angiography, avoiding the risk of its unpredictable impact on platelet function. Taking into account that morphine negatively affects the absorption of ticagrelor from the gastrointestinal tract, we assumed that addition of an opioid antagonist, naloxone administered orally, would contribute to the optimization of the PK/PD profile of ticagrelor and its active metabolite. As assessed in previous studies, a group of 15 patients for each study arm was considered to be sufficient for statistical analysis.

Blood sample collection

According to the study protocol, following obtainment of informed consent for participation in the study and randomization into the study arms, collection of blood samples for the pharmacokinetic and pharmacodynamic assessment was done. Nine predefined time points of blood sampling were as follows: before the administration of ticagrelor loading dose and 15 min, 30 min, 45 min, 1 h, 2 h, 3 h, 4 h, 6 h after its administration.

Pharmacokinetics

Pharmacokinetic assessment was performed for each study participant at all predefined time points. Plasma concentrations of ticagrelor and its active metabolite were evaluated in The Department of Medicinal Chemistry, Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz using liquid chromatography and mass spectrometry. Measurements were performed using Shimadzu UPLC Nexera X2 system and Shimadzu 8030 ESI-Triple

Quadrupole mass spectrometer. The limits of quantification for ticagrelor and its active metabolite were defined as 4.69 ng/mL.

Pharmacodynamics

The evaluation of pharmacodynamics was performed using the Multiplate analyzer (ADPtest, Roche Diagnostics, Switzerland). The measurements of platelet reactivity were conducted with multiple electrode aggregometry (MEA) at all time points as mentioned above. Area under the aggregation curve (AUC) as a parameter reflecting the overall exposure to both ticagrelor and AR-C124900XX, was assessed on the assumption that AUC > 46 units (U) was defined as high platelet reactivity (HPR).

Study outcomes

According to the protocol, the primary endpoint of this PK/PD study was the time required to reach the maximum plasma concentration of ticagrelor and AR-C124900XX following ticagrelor loading dose intake. Secondary endpoints included maximum concentration of ticagrelor and its metabolite, area under the plasma concentration-time curve (AUC_{CT}) for ticagrelor and AR-C124900XX and platelet reactivity assessed by MEA in the aforementioned time points. The complete list of study outcomes is presented in Figure 2.

Statistical analysis

Statistical analysis was performed using Matlab R2014 Software (Mathworks, Natick, MA, USA), the Statistica 12.5 package (StatSoft, Tulsa, OK, USA) and R version 3.5.0 (R: library lme). $P < 0.05$ were considered statistically significant. AUC was calculated using the trapezoidal rule. Comparative analysis of pharmacokinetic parameters between the study arms and time points were conducted using mixed models with random effects with the maximum likelihood method applied for estimating variance parameters. Comparison of pharmacodynamic parameters between the study arms was performed with the Fisher exact test.

Results

Population baseline characteristics

Between October 2016 and December 2018, a total of 30 unstable angina (UA) patients were enrolled in the study. Baseline serum troponin evaluation required ruling out an acute myocardial infarction was performed for each study participant showing no case of

elevation above the reference level of 34.5 ng/L and 15.6 ng/L for men and women, respectively. The study population was generally well balanced, except for the prevalence of prior coronary artery disease and consequently prior percutaneous coronary intervention (PCI), which were noticeably higher in the study arm (66.7% vs. 28.6%, $p = 0.04$ and 53.3% vs. 14.3%, $p = 0.03$, respectively). The study population baseline characteristics are presented in Figure 3.

Safety and tolerability evaluation

The safety evaluation did not reveal any case of serious adverse events such as death, myocardial infarction, stent thrombosis, stroke or thromboembolic events throughout the study. Minor symptoms including weakness and headache were reported by 2 patients in the active arm. On the other hand, adverse effects in the control group of participants included mild bradycardia (50–55 bpm), nausea (2 patients) and excessive sweating associated with feeling unwell (1 patient). Due to vomiting that required immediate administration of metoclopramide, a prokinetic drug, 1 patient's participation in the trial was terminated, which resulted in exclusion of the initially obtained results of pharmacokinetics and pharmacodynamics of this participant from statistical analysis.

Pharmacokinetics

Pharmacokinetic assessment was performed for each study participant. Statistical analysis of all results showed only a trend toward a better PK profile in the naloxone arm. Mixed models with random effects showed no significant differences between the study arms in terms of ticagrelor-related parameters. However, the difference between plasma concentrations of AR-C124910XX obtained at 120 min following ticagrelor LD reached statistical significance ($p=0.0417$). PK parameters obtained throughout the study are presented in Figure 4. Mean concentration of ticagrelor and its active metabolite is presented in Figures 5 and 6.

Pharmacodynamics

The PD evaluation was performed for each patient, revealing no significant differences between the study arms. The superiority of the naloxone arm in terms of percentage of HPR patients at particular time points patients was only numerical. The most pronounced difference was observed at 30 minutes following ticagrelor LD (7 vs. 10 patients) for the naloxone and control arm respectively ($p = 0.18$; Fig. 7).

Discussion

The recent discovery of the so-called ‘morphine effect’ brought new challenges into contemporary ACS treatment strategies. As mentioned before, co-administration of morphine in the course of ACS is no longer a first-line approach due to its negative impact on P2Y₁₂ receptor inhibitors PK/PD profile. Inevitably, some patients, especially presenting with STEMI, will require strong analgesic agents to relieve unbearable pain associated with the infarction. Until now, several approaches to reduce ‘the morphine effect’ have been described in the literature.

The present study is the first one aiming to assess the influence of oral naloxone on ticagrelor and AR-C124900XX in ACS patients who received morphine. The results show no definite benefit in terms of the PK and PD profile of ticagrelor in the naloxone arm, however a trend toward improvement of analyzed parameters could be observed.

In one previous study it was proved that co-administration of an anti-emetic agent, metoclopramide, leads to higher plasma concentrations of ticagrelor and its active metabolite and reduction of time required to reach maximum plasma concentrations of ticagrelor and its metabolite (123 min vs. 168 min for control arm, $p = 0.015$) [19].

The PK/PD profile of currently used P2Y₁₂ receptor inhibitors has also been found to be noticeably dependent on the administration strategy of the drug. No inconsistencies can be found in terms of the administration of crushed tablets of P2Y₁₂ inhibitors. Zafar et al. proved that the administration of clopidogrel in healthy volunteers was associated with faster and greater bioavailability if the drug was given as a crushed form via a nasogastric tube [20]. According to a study by Rollini et al. [21], administration of crushed prasugrel in STEMI patients led to faster absorption of this agent. Also, it was associated with higher plasma concentrations of its metabolite and reduction of platelet reactivity 30 min after the LD of prasugrel. In the MOHITO study, Parodi et al. [22] reported that the time required to achieve platelet inhibition in STEMI patients was significantly shorter if they received crushed ticagrelor instead of standard integral tablets. Oral administration of crushed ticagrelor was also associated with the best PK/PD profile of ticagrelor and its active metabolite in a previous study evaluating the influence of ticagrelor administration strategy in patients presenting with UA. Moreover, the above-mentioned study demonstrated this strategy to be superior over sublingual administration of crushed ticagrelor [18].

The results of the latest studies aiming to evaluate the impact of ticagrelor administration strategy on its PK/PD profile show superiority of chewed ticagrelor in terms of

platelet reactivity units (PRU) measured with VerifyNow in non-STEMI patients at 1 hour where it was found to be significantly lower [23]. In a study by Venetsanos et al. [24] PRU were also significantly lower in patients presenting with stable angina pectoris in the chewed-ticagrelor arm in comparison with integral ticagrelor arm.

Limitations of the study

The study population comprised only unstable angina patients, thus baseline platelet reactivity does not fully reflect characteristics of STEMI patients. A limited number of study participants might have negatively influenced the statistical analysis as only a trend toward improvement of the PK profile could be observed in the naloxone arm. Although the prevalence of prior coronary artery disease in the naloxone group was higher than in the control group, it did not affect baseline platelet reactivity.

Conclusions

According to available research, this study is the first one to evaluate the impact of an anti-opioid drug, naloxone, on PK and PD of ticagrelor and its active metabolite. Even though a trend toward improvement of the PK/PD profile of ticagrelor in ACS patients pre-treated with morphine followed by oral naloxone is perceptible, further research is required to determine optimal approaches to overcome the ‘morphine effect’.

Conflict of interest: Malwina Barańska received honoraria for lectures from Astra Zeneca. Bernd Jilma has served as a consultant to and in advisory boards of AstraZeneca. Jacek Kubica delivered a lecture for AstraZeneca. All of the other authors declare no potential conflict of interests regarding publication of this paper.

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Figure 1. A complete list of inclusion/exclusion criteria for the study.

Inclusion criteria (all criteria must be met)
Provision of informed consent prior to any study specific procedures
Diagnosis of unstable angina
Male or non-pregnant female, aged 18–80 years
Provision of informed consent for angiography and percutaneous coronary intervention
GRACE score < 140 patients
Exclusion criteria (none of the criteria can be met)
Treatment with ticlopidine, clopidogrel, prasugrel or ticagrelor within 14 days before study enrollment
Current treatment with morphine or any opioid “mi” receptor agonist
Hypersensitivity to ticagrelor
Current treatment with oral anticoagulant or chronic therapy with low-molecular-weight heparin
Active bleeding
History of intracranial hemorrhage
Recent gastrointestinal bleeding (within 30 days)
History of coagulation disorders
Platelet count less than $100 \times 10^3/\text{mcl}$
Hemoglobin concentration less than 10.0 g/dL
History of moderate or severe hepatic impairment
History of major surgery or severe trauma (within 3 months)
Risk of bradycardic events as judged by the investigator
Second- or third-degree atrioventricular block during screening for eligibility
History of asthma or severe chronic obstructive pulmonary disease
Kidney disease requiring dialysis
Manifest infection or inflammatory state
Killip class III or IV during screening for eligibility
Respiratory failure
History of severe chronic heart failure (NYHA class III or IV)
Concomitant therapy with strong CYP3A inhibitors (ketoconazole, itraconazole, voriconazole, telithromycin, clarithromycin, nefazadone, ritonavir, saquinavir, nelfinavir,

indinavir, atazanavir) or strong CYP3A inducers (rifampicin, phenytoin, carbamazepine, dexamethasone, phenobarbital) within 14 days and during study treatment
Body weight below 50 kg

Figure 2. Complete list of study outcomes.

Study primary outcome
Time to maximum concentration (t_{max}) for ticagrelor and AR-C124900XX
Study secondary outcomes
Maximum ticagrelor and AR-C124900XX concentration
Area under the plasma concentration-time curve for ticagrelor (AUC 0–6 h)
Area under the plasma concentration-time curve for AR-C124900XX (AUC 0–6h)
Platelet reactivity assessed by multiple electrode aggregometry

Figure 3. Study population baseline characteristics.

	Study group (%) [n = 15]	Control group (%) [n = 14]	P
Age [years]	66.87*	60.21*	0.56
Male	12 (80)	7 (50)	0.089
Body weight [kg]	88.73*	77.48*	0.25
Body mass index [kg/m ²]	29.05*	27.24*	0.89
Prior CAD	10 (66.7)	4 (28.6)	0.04
Prior AMI	8 (53.3)	3 (21.4)	0.08
Prior PCI	8 (53.3)	2 (14.3)	0.03
Prior CABG	3 (20.0)	3 (21.4)	0.95
Arterial hypertension	12 (80.0)	9 (64.3)	0.34
Prior peptic ulcer disease	3 (20.0)	1 (7.1)	0.31
Prior GI bleeding	1 (6.7)	1 (7.1)	0.96
Prior stroke/TIA	2 (13.3)	1 (7.1)	0.59
CKD	0	1 (7.1)	0.29
Hyperlipidemia	13 (86.7)	12 (85.7)	0.94
Current smoker	1 (6.7)	3 (21.4)	0.23
History of smoking	8 (53.3)	4 (28.6)	0.18
Family history of CAD	5 (33.3)	9 (64.3)	0.09
Diabetes mellitus	3 (20.0)	4 (28.6)	0.59
Insulin therapy	0	3 (21.4)	0.06
COPD	0	1 (7.1)	0.30
Peripheral atherosclerosis	3 (20.0)	2 (14.3)	0.68

*Data are shown as mean. AMI — acute myocardial infarction; CABG — coronary artery bypass grafting; CKD — chronic kidney disease; COPD — chronic obstructive pulmonary disease; CAD — coronary artery disease; EF — ejection fraction; PCI — percutaneous coronary intervention; TIA — transient ischemic attack

Figure 4. Pharmacokinetic parameters of ticagrelor and AR-C124910XX in mixed model with random effects.

	Value	Standard error	P-value
Ticagrelor			
Intercept	-274.1965	184.04303	0.1377
Time 15 vs. time 0	14.0322	223.66104	0.9500
Time 30 vs. time 0	145.4685	223.66104	0.5161
Time 45 vs. time 0	451.1968	223.66104	0.0449
Time 60 vs. time 0	762.1987	223.66104	0.0008
Time 120 vs. time 0	694.5401	223.66104	0.0022
Time 180 vs. time 0	880.6841	223.66104	0.0001
Time 240 vs. time 0	832.2042	223.66104	0.0003
Time 360 vs. time 0	589.4043	223.66104	0.0090
Group I vs. group II	79.2077	45.08410	0.0803
Time 15 group	5.8586	58.01639	0.9197
Time 30 group	30.3315	58.01639	0.6016
Time 45 group	40.3730	58.01639	0.4872
Time 60 group	31.6464	58.01639	0.5860
Time 120 group	82.9364	58.01639	0.1543
Time 180 group	-7.0878	58.01639	0.9029
Time 240 group	-4.6060	58.01639	0.9368
Time 360 group	24.9611	58.01639	0.6674
Metabolite			
Intercept	-48.18294	39.93862	0.2290
Time 15 vs. time 0	0.00000	49.98636	1.0000
Time 30 vs. time 0	-3.58612	49.98636	0.9429
Time 45 vs. time 0	17.25228	49.98636	0.7303
Time 60 vs. time 0	66.51414	49.98636	0.1847
Time 120 vs. time 0	160.11218	49.98636	0.0016
Time 180 vs. time 0	229.63223	49.98636	0.0000
Time 240 vs. time 0	258.55988	49.98636	0.0000
Time 360 vs. time 0	177.13110	49.98636	0.0005
Group I vs. group II	13.79099	9.97219	0.1681
Time 15 group	0.00000	12.96617	1.0000
Time 30 group	4.96449	12.96617	0.7022
Time 45 group	14.83565	12.96617	0.2538
Time 60 group	19.00707	12.96617	0.1441
Time 120 group	26.55748	12.96617	0.0417
Time 180 group	6.51674	12.96617	0.6158
Time 240 group	-4.16173	12.96617	0.7485
Time 360 group	8.45659	12.96617	0.5150

Figure 5. Mean ticagrelor plasma concentration throughout the study; tica — ticagrelor; mf — morphine.

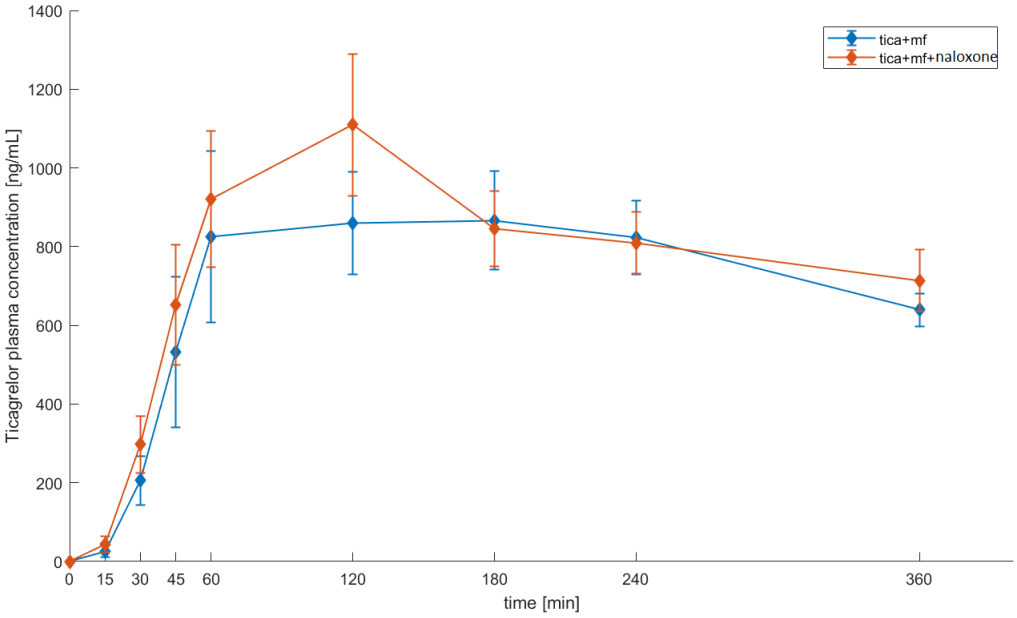


Figure 6. Mean concentration of the active metabolite, AR-C124910XX throughout the study; tica — ticagrelor; mf — morphine.

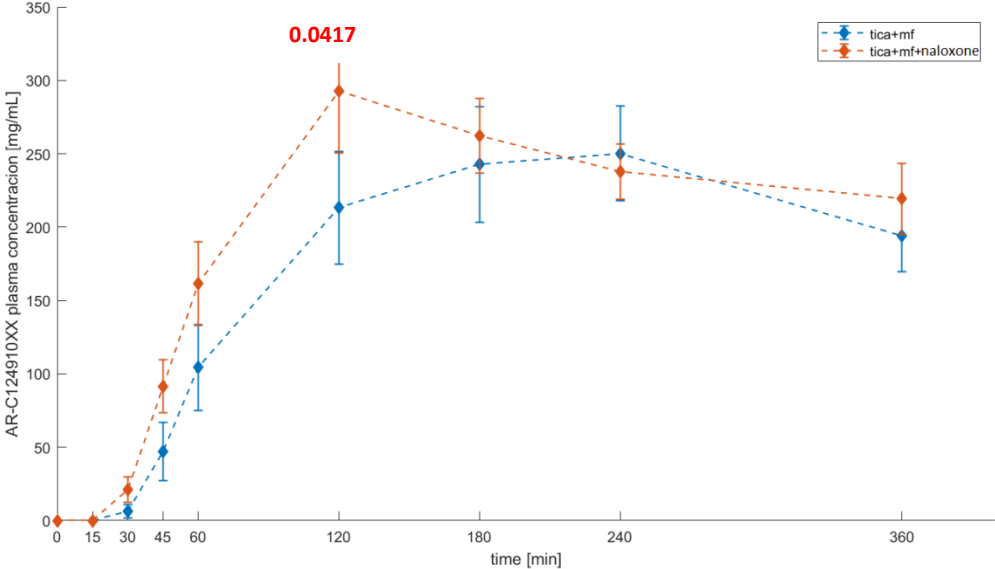


Figure 7. Proportion of patients with high platelet reactivity in study time points.

