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The Kinetics of Integrilin Limited by Obesity (KILO): A Multicenter Randomized Pharmacokinetic and Pharmacodynamic Clinical Trial

John P. Vavalle, MD^{*,†}, Susanna R. Stevens, MS[†], Nancy Hassinger, MD[‡], Mauricio G. Cohen, MD[§], Anita Arnold, DO^{||}, David E. Kandzari, MD[¶], Frank V. Aguirre, MD[#], Daniel D. Gretler, MD^{**}, and John H. Alexander, MD, MHS^{*,†}

^{*}Duke University Medical Center, Durham, NC

[†]Duke Clinical Research Institute, Durham, NC

[‡]St. Mary's Medical Center, Duluth, MN

[§]University of Miami Miller School of Medicine, Miami, FL

^{||}Cardiovascular Associates, Milwaukee, WI

[¶]Piedmont Heart Institute, Atlanta, GA

[#]Prairie Cardiovascular Consultants, Southern Illinois University School of Medicine, Springfield, IL

^{**}Portola Pharmaceuticals, San Francisco, CA

Abstract

Background—KILO tested 2 novel weight-based eptifibatide dosing strategies compared with standard dosing in obese patients undergoing elective percutaneous coronary intervention (PCI). Eptifibatide dosing is weight-adjusted for patients up to 121 kg. Patients above this weight receive the same maximal dose, although it is unknown if this provides adequate eptifibatide concentration or platelet inhibition.

Methods—Sixty-seven patients weighing 125 kg undergoing elective PCI were randomized to 1 of 3 eptifibatide dosing regimens: standard dosing using a weight of 121 kg, actual body weight-based (ABW) dosing with no upper limit, or ideal body weight-based (IBW) dosing. Boluses of 180 µg/kg were given 10 minutes apart, followed by a 2.0 µg/kg/min infusion. Plasma eptifibatide concentrations were drawn at 12–18 hours after initiating the infusion. Platelet aggregation was assessed at baseline and 10 minutes after the second bolus.

Results—Sixty-seven patients were randomized to standard (n=22), ABW (n=23), or IBW (n=22) dosing. The median (25th, 75th) steady-state plasma eptifibatide concentrations were 1740

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Address for correspondence: John H. Alexander, MD, MHS, Duke Clinical Research Institute, Duke University Medical Center, 2400 Pratt Street, Durham, NC 27705. Phone: (919) 668-8955; Fax: (919) 668-7085. john.h.alexander@duke.edu. .

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ng/mL (1350, 2350), 1780 ng/mL (1510, 2350), and 1055 ng/mL (738, 1405), respectively ($P<0.001$). Ten-minute median (25th, 75th) platelet aggregation units were 7 (0, 21), 2 (0, 8), and 14 (8, 20), respectively, ($P=0.001$).

Conclusions—ABW eptifibatide dosing leads to higher plasma concentrations and greater platelet inhibition than standard or IBW dosing in obese patients undergoing PCI. Current recommendations for eptifibatide dosing may be inadequate in patients >121 kg. Further study is warranted to define the optimal dosing of eptifibatide and other medications in obese patients.

Keywords

eptifibatide; obesity; pharmacokinetics; pharmacodynamics; platelet inhibition

Eptifibatide, an intravenous platelet glycoprotein IIb/IIIa inhibitor (GPI), has been shown to reduce ischemic complications during percutaneous coronary intervention (PCI). The level of platelet aggregation inhibition achieved with intravenous GP IIb/IIIa inhibitors is dependent on the dosage and plasma concentration. The pharmacodynamic goal of at least 80% inhibition of the GP IIb/IIIa receptor, as determined by light transmission aggregometry, is the level thought necessary to prevent ischemic complications following PCI.³⁻⁵ The Platelet Aggregation and Receptor Occupancy with Integrilin—Dynamic Evaluation (PRIDE) study identified the 180/2.0/180 dose (180 μ g/kg bolus followed a second 180 μ g/kg bolus 10 minutes later and a 2.0 μ g/kg/minute infusion) as the dose necessary to achieve and maintain $>80\%$ occupancy of the GP IIb/IIIa receptor.^{2,6-8} The plasma concentration necessary to achieve this pharmacodynamic effect was found to be approximately 1600 ng/mL.⁷ More recently, the GOLD study found that platelet inhibition of $<95\%$ using a point-of-care test was associated with a significantly higher risk of death, myocardial infarction, or target lesion revascularization.⁹

A meta-analysis of over 10,000 patients from 22 studies evaluated the efficacy and safety of glycoprotein IIb/IIIa inhibitors during elective PCI. They found that the use of GPIs, even in the current era of drug eluting stents and thienopyridine use reduced nonfatal myocardial infarctions without an increase in major bleeding. However, there was an increase in minor bleeding and no difference in all-cause mortality.¹⁰

Studies evaluating eptifibatide had an upper weight limit above which patients received the same fixed dose regardless of their weight. In the IMPACT-II (Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis-II) and ESPRIT (Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy) trials, this limit was 143 and 146 kg, respectively. In the PURSUIT (Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy) trial, patients weighing >121 kg received a fixed maximal dose.¹² Current eptifibatide labeling for PCI recommends that patients weighing

121 kg receive the weight-adjusted 180/2.0/180 double bolus and infusion regimen, and patients weighing >121 kg receive the fixed maximal dose of 22.6 mg boluses and a 15 mg/hour infusion.

Many patients who undergo PCI weigh >121 kg. In these patients, it is unknown if dosing based on current recommendations is sufficient to achieve therapeutic steady-state plasma drug concentrations or 80% platelet inhibition. Thus, obese patients may receive additional benefit from a dosing regimen that is adjusted for actual body weight (ABW) and allows continued upward dose adjustment for incremental increases in weight above 121 kg. Alternatively, since eptifibatide has a limited volume of distribution and does not distribute well into adipose tissue, obese patients may be better suited with lower, ideal body weight (IBW)-adjusted dosing. The objective of KILO was to compare an ABW-based dosing regimen and an IBW-based dosing regimen with the current standard dosing in patients

weighing >125 kg as assessed by plasma eptifibatide concentrations and inhibition of platelet aggregation.

METHODS

Patients

Sixty-seven obese patients weighing >122 kg scheduled to undergo elective PCI with planned stenting and use of eptifibatide were randomized to 1 of 3 dosing regimens. Exclusion criteria were thrombolytic therapy within 24 hours of randomization, ongoing chest pain or hemodynamic instability requiring urgent PCI, treatment with a GP IIb/IIIa inhibitor in the 30 days prior to randomization, stroke or transient ischemic attack within 30 days, any history of a hemorrhagic stroke or bleeding diathesis, current active bleeding, thrombocytopenia with a platelet count $<120 \times 10^9/L$, major surgery within the previous 6 weeks, uncontrolled hypertension (systolic blood pressure >200 mm Hg or diastolic blood pressure >110 mm Hg), serum creatinine >2.0 mg/dL, or the use of any investigational drug or device in the previous 30 days. Five sites enrolled patients into this trial: St. Luke's Medical Center, Milwaukee, WI; Duke University Medical Center, Durham, NC; University of North Carolina Hospitals, Chapel Hill, NC; Prairie Cardiovascular Consultants, Southern Illinois University School of Medicine, Springfield, IL; and St. Mary's Medical Center, Duluth, MN. Institutional review board approval was obtained at all centers and all patients gave informed consent prior to participation. This study was funded by a grant from Schering-Plough Corp., now Merck-Schering-Plough. The authors are solely responsible for the design and conduct of this study; all study analyses, the drafting and editing of the paper and its final contents.

Randomization and Treatment

Patients were enrolled in this prospective randomized single-blind clinical trial at 5 participating centers in the United States. Prior to randomization, baseline demographics and clinical and laboratory data, including baseline platelet aggregation, were collected for each patient (Table 1). Prior to PCI, patients were randomized by sealed envelope in a 1:1:1 fashion to 1 of 3 open-label eptifibatide-dosing regimens: 1) standard dosing with two 22.6 mg boluses at 0 and 10 minutes and a 15 mg/hour infusion started at time of first bolus and continued for 12–18 hours; 2) ABW-adjusted dosing without an upper limit with two 180 $\mu\text{g/kg}$ boluses at 0 and 10 minutes and a 2.0 $\mu\text{g/kg/minute}$ infusion started at time of first bolus and continued for 12–18 hours; or 3) IBW-adjusted dosing with two 180 $\mu\text{g/kg}$ boluses at 0 and 10 minutes and 2.0 $\mu\text{g/kg/minute}$ infusion started at time of first bolus and continued for 12–18 hours. Randomization was stratified by site and by patient weight ($<$ or >140 kg). ABW dosing used the patient's actual body weight. IBW dosing used the patient's ideal body weight which was calculated using the formula: $50 + 2.3 \text{ kg/inch over } 5 \text{ feet}$ for men, and $45.5 + 2.3 \text{ kg/inch over } 5 \text{ feet}$ for women.

PCI procedures were performed per local standards at each participating institution. Unfractionated heparin was administered as needed to attain the recommended target activated clotting time of 200–250 seconds.

Assessment of Platelet Function

Platelet aggregation in response to thrombin activated peptide agonist was assessed prior to administration of the first eptifibatide bolus and 10 minutes after administration of the second bolus. Each blood sample was collected from an arterial sheath into a 3 mL partial-draw Li^{2+} heparin-coated tube. An Ultegra Rapid Platelet Function Analyzer point-of-care device (Accumetrics, Inc., San Diego, CA) was used at the bedside to measure platelet aggregation.¹³

Pharmacokinetic Assessment

One blood sample was obtained from each patient for measurement of steady-state eptifibatide concentration. Samples were collected from a peripheral vein into pre-chilled 10 mL EDTA tubes 12–18 hours after the start of infusion and while the infusion was still running. Each sample was centrifuged at 5°C for 20 minutes at 1000 g within 20 minutes of blood collection. A total of 1.8 mL of plasma was then transferred in duplicate to polypropylene vials containing 0.2 mL of 8.5% phosphoric acid to stabilize the eptifibatide during frozen storage. Samples were sent to a core laboratory (MDS Pharma Services, Inc., Montreal, Quebec) for analysis of steady-state plasma eptifibatide concentration using mass spectrometry.

Pharmacokinetic, Pharmacodynamic, and Clinical Endpoints

The primary endpoint for this study was steady-state plasma eptifibatide concentrations 12–18 hours after the eptifibatide infusion had begun. Secondary endpoints included the level of platelet aggregation inhibition achieved 10 minutes after the second bolus of eptifibatide. Patients were followed for the duration of the index hospitalization for the occurrence of any of the following: death, periprocedural myocardial infarction (defined as a CK-MB at least 3 × upper limit of normal), need for target vessel revascularization, bleeding assessed according to the TIMI scale, transfusion, and thrombocytopenia.¹⁴

Statistical Methods and Sample Size Calculations

Pairwise comparisons of the proportion of patients achieving a steady-state eptifibatide concentration of at least 1600 ng/mL across the 3 randomized treatment arms were tested using Pearson chi-square tests for the 2 experimental dosing regimens versus the standard. The relationships between patient weight and eptifibatide concentration, dosing regimens and concentrations, and the differential effect of dosing regimen across increasing weight were compared using analysis of covariance (ANCOVA) models for concentration that included weight, dosing regimen, and the weight-by-dosing regimen interaction. In the presence of a statistically significant ($P < 0.05$) overall interaction term, pairwise interactions are presented for each of the novel regimens versus the standard. A scatterplot of concentration by weight with the 3 regression lines for each dosing regimen based on the ANCOVA model is presented (Figure 1). The change in platelet aggregation pre- to post-drug was compared between dosing regimens using ANCOVA where weight and level of platelet aggregation pre-drug were included as covariates.

Data were analyzed using SAS software, version 9 (SAS Institute Inc., Cary, NC). Baseline characteristics, treatment characteristics, and adverse events are presented by dosing regimen as median (25th, 75th percentile) for continuous variables and as frequencies with their respective percentages for categorical variables. A 2-sided P value of 0.05 was considered statistically significant in all analyses. No adjustments were made for multiple comparisons, recognizing the hypothesis-generating nature of this study.

RESULTS

A total of 67 patients were enrolled: 22 in the standard dosing group, 23 in the ABW dosing group, and 22 in the IBW dosing group. Most of the patients were female and the median (25th, 75th percentile) weight was 140 (129, 156) kg. The median weight, age, and baseline creatinine were similar across dosing groups (Table 1). Pre-drug median platelet aggregation units were 161 (143, 228) in the standard dosing group, 180 (122, 216) in the ABW dosing group, and 183 (152, 229) in the IBW dosing group (Table 2).

All patients in the standard dosing group received bolus eptifibatide doses of 22.6 mg. In the ABW and the IBW dosing groups, the median bolus doses were 25.4 (23.0, 26.6) mg and 13.4 (12.0, 14.0) mg, respectively. The infusion rate in the standard dosing group was fixed at 15 mg/hour in all patients. The median infusion rate was 17.0 (15.4, 17.8) mg/hour in the ABW group and 8.9 (8.0, 9.3) mg/hour in the IBW group (Table 2).

Median plasma eptifibatide concentrations in the ABW dosing regimen were similar to standard dosing, while IBW dosing resulted in significantly lower concentrations than standard dosing (Table 2). For 6 subjects, eptifibatide concentrations were missing or not received and were not included in the analyses. The proportion of patients achieving eptifibatide concentrations above 1600 ng/mL was highest in the ABW dosing group (64%), and lowest in the IBW group (10%) (Table 3).

Eptifibatide concentrations across the spectrum of patient weights are shown in Figure 1. The relationship between weight and plasma concentration differed in the 3 dosing regimens (weight-by-regimen interaction P value=0.034). Standard dosing resulted in decreasing plasma concentrations with increasing body weight, while ABW dosing resulted in increasing plasma concentrations with increasing weight (slope for standard= -6.4, slope for ABW=20.6, interaction P value=0.011). IBW dosing resulted in a change in plasma eptifibatide concentrations with similar magnitude but opposite direction to standard dosing across the range of weights (slope=6.9), though not significantly different than standard dosing (weight-by-regimen interaction P value=0.240). The plot in Figure 1 shows that the regression lines of standard and ABW dosing cross at approximately 144 kg. This suggests that as weight increases beyond 144 kg there is a growing difference in serum eptifibatide concentrations between standard and ABW dosing, with standard dosing leading to substantially lower serum concentrations than ABW dosing as weight increases.

Platelet aggregation decreased after eptifibatide administration in all groups. In the standard dosing group, post-drug platelet aggregation fell to a median of 7 (0, 21) from 161 (143, 228) measured before drug administration. In the ABW group, platelet aggregation fell to 2 (0, 8) from 180 (122, 216), and in the IBW group it decreased to 14 (8, 20) from 183 (152, 229). The decrease in platelet aggregation from pre- to post-drug was significantly greater in the ABW regimen than the standard regimen (P =0.046, adjusted for pre-drug platelet aggregation and weight). IBW dosing did not result in significantly greater platelet inhibition than standard dosing (P =0.176). The median percent platelet inhibition was similar among all 3 dosing strategies (Table 2). Figure 2 shows the platelet aggregation units for each subject pre- and post-eptifibatide dosing in the (a) standard, (b) ABW, and (c) IBW dosing groups. Data were missing for 1 subject from each group for pre-drug aggregation and for 1 subject from the ABW group for post-drug aggregation.

Clinical outcomes are shown in Table 4. Two patients experienced TIMI minor bleeds, 1 experienced a TIMI major bleed, and 1 required a blood transfusion in the standard dosing group. One patient experienced a TIMI minor bleed in the ABW group. There was 1 in-hospital death and 2 periprocedural myocardial infarctions, all in the IBW group.

DISCUSSION

We found that current standard eptifibatide dosing may not provide adequate eptifibatide concentrations in obese patients. As expected, higher concentrations were associated with higher doses of eptifibatide. Standard dosing resulted in a trend toward decreasing plasma concentrations of eptifibatide with increasing patient body weight. ABW-based dosing resulted in increasing eptifibatide concentrations in heavier patients. This suggests that the best dosing regimen to provide consistent inhibition of platelet aggregation across a range of

patient weights would likely be closer to ABW dosing than the currently recommended dosing strategy. However, ABW dosing provides increased plasma concentrations with increasing weight leading to potential overdosing in the heaviest patients. A dose that provides a constant plasma level of eptifibatide of at least 1600 ng/mL would be ideal; however, this would likely require different dosing regimens for patients with different weights.

IBW dosing failed to achieve the pharmacokinetic target of an eptifibatide concentration of >1600 ng/mL thought necessary to prevent ischemic complications following PCI. Furthermore, IBW dosing also failed to achieve the pharmacodynamic target of 95% platelet inhibition that was determined by the GOLD study as the threshold thought necessary to reduce ischemic events using the same point-of-care test.⁹ This group also had the flattest eptifibatide / weight relationship consistent with the known distribution of eptifibatide primarily into the plasma compartment.¹⁵ In addition, although this study was not powered to significantly detect differences in clinical outcomes, all of the periprocedural myocardial infarctions and in-hospital deaths occurred in the IBW dosing group. Despite higher plasma concentrations of eptifibatide in the ABW dosing group, no increase in bleeding was observed.

Another important measure of the effect of eptifibatide is the platelet glycoprotein IIb/IIIa receptor occupancy. The Intracoronary Eptifibatide (ICE) Trial evaluated the effect of intracoronary eptifibatide versus intravenous eptifibatide and showed a significantly higher level of GP IIb/IIIa receptor occupancy in the local coronary bed, as measured in the coronary sinus, with intracoronary administration.¹⁶ This was associated with improved microvascular perfusion, with the only multivariate predictor of improved perfusion being GP IIb/IIIa receptor occupancy after the first bolus. This study underscores the importance of adequate dosing and the need to achieve a high level of receptor occupancy to reduce ischemic events. In the obese patient, this high level of receptor occupancy is less likely to be achieved with current dosing recommendations.

The appropriate dosing of antithrombotics in obese patients has been poorly studied. Despite evidence that current dosing recommendations for medications such as clopidogrel may be insufficient to achieve target effect in obese patients, there is little guidance available for dosing strategies in the obese.¹⁷ In fact, the labeled guidelines for clopidogrel, prasugrel, abciximab, and enoxaparin administration do not specifically address dosing in obese patients. For tirofiban and bivalirudin, there are dosing recommendations for patients weighing up to 153 kg and 152 kg, respectively, but no specific guidelines beyond that weight. Likewise, for unfractionated heparin, weight-based dosing nomograms are often used with maximum dosing limits leading to possible under-dosing in morbidly obese patients.

There are several important limitations to this study. The study was not powered to assess the effect of different dosing regimens on clinical outcomes. By design, detailed information on baseline characteristics, co-morbidities and concomitant medications was not collected. Although patients were randomized in this study, a baseline imbalance of relevant factors cannot be excluded. Platelet aggregation was tested using only one type of device. It is possible that the use of another assay may yield different results. Information on platelet count, either before or after eptifibatide administration was not recorded. Serial platelet aggregation assessments, especially in light of the small sample size, would have provided more insight into the pharmacodynamics of eptifibatide over time, but this was not done in this study.

Conclusion

In obese patients undergoing PCI, current eptifibatide dosing recommendations may not achieve target serum concentrations thought necessary to prevent ischemic complications. ABW eptifibatide dosing leads to higher steady-state concentrations and greater suppression of platelet aggregation than the current standard or IBW dosing regimens. Our study suggests that ABW dosing may be preferable and should be considered in obese patients undergoing PCI, while IBW dosing should be avoided due to under-dosing. Further study is warranted to define the optimal dosing of eptifibatide and other antithrombotic therapies in obese patients.

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Figure 1.

Plasma concentrations of eptifibatide in the 3 dosing regimens across the spectrum of weights. Black dots and solid black line correspond to standard dosing; open circles and dashed line correspond to weight-based dosing; gray dots and solid gray line correspond to ideal body weight-based dosing. Standard dosing: slope= -6.4 , Weight-based dosing: slope= 20.6 , Ideal weight-based dosing: slope= 6.9 . One patient with weight 247 kg and eptifibatide concentration 1350 ng/mL is not shown but is included in all calculations.

Figure 2.

Pre- and post-eptifibatide platelet aggregation units in for each patient in the standard dosing group (a), ABW dosing group (b), and IBW dosing group (c).

Table 1

Baseline characteristics

Baseline Characteristics	Standard Dosing (N=22)	ABW-Based Dosing (N=23)	IBW-Based Dosing (N=22)	All (N=67)	P Value
Age, yrs	60 (49, 63)	56 (52, 58)	56 (50, 61)	57 (51, 62)	0.588
Male, no. (%)	4 (18.2)	3 (13.0)	6 (27.3)	13 (19.4)	0.469
Weight, kg	139 (129, 157)	141 (128, 148)	139 (132, 156)	140 (129, 156)	0.857
Ideal weight, kg	73 (66.2, 75.4)	71 (63.9, 73.1)	71 (63.9, 73.1)	71 (63.9, 73.1)	0.538
Height, in	72 (69, 73)	71 (68, 72)	70 (68, 72)	71 (68, 72)	0.603
Baseline creatinine, mg/dL [*]	1.1 (0.9, 1.2)	0.9 (0.8, 1.0)	1.0 (0.8, 1.2)	1.0 (0.8, 1.2)	0.197
Body Mass Index (BMI)	44.2 (39.7, 51.0)	43.7 (40.6, 49.6)	46.6 (41.4, 49.5)	44.6 (40.7, 49.6)	0.872

Values are presented as median (25th, 75th) unless otherwise indicated. ABW indicates actual body weight; IBW, ideal body weight.

^{*} One patient in the standard dosing group had a missing creatinine value.

Table 2

Eptifibatide dosing, plasma concentrations and pre- and post-drug platelet aggregation units

	Standard Dosing (N=22)	ABW-Based Dosing (N=23)	IBW-Based Dosing (N=22)	All (N=67)	<i>P</i> Value Across Dosing Groups	<i>P</i> Value for Standard vs. ABW
Eptifibatide bolus, mg	22.6 (22.6, 22.6)	25.4 (23.0, 26.6)	13.4 (12.0, 14.0)	22.6 (14.0, 23.2)	<0.001	<0.001
Eptifibatide infusion rate, mg/hr	15 (15, 15)	17.0 (15.4, 17.8)	8.9 (8.0, 9.3)	15.0 (9.3, 15.5)	<0.001	<0.001
Eptifibatide concentration, ng/mL *	1740 (1350, 2350)	1780 (1510, 2350)	1055 (738, 1405)	1520 (1140, 2020)	<0.001	0.927
Pre-drug PAU †	161 (143, 228)	179.5 (122, 216)	183 (152, 229)	174 (142, 224.5)	0.613	0.653
Post-drug PAU ‡	7 (0, 21)	2 (0, 8)	14 (8, 20)	7.5 (0, 19)	0.001	0.051
Percent Platelet Inhibition ‡	96.2 (90.9, 100.0)	98.2 (95.1, 100.0)	93.1 (88.4, 96.7)	95.8 (91.7, 100.0)	0.004	0.130

ABW indicates actual body weight; IBW, ideal body weight; PAU, platelet aggregation units. Values presented as median (25th, 75th).

* Eptifibatide concentrations missing for 6 patients.

† Pre-drug PAU missing for 3 patients (1 in each dosing group).

‡ Post-drug PAU values missing for 1 patient in ABW dosing group.

Table 3

Patients in each dosing group achieving plasma concentrations >1600 ng/mL

	Standard Dosing (N=19)	ABW-Based Dosing [*] (N=22)	IBW-Based Dosing [†] (N=20)
Eptifibatide 1600 ng/mL	9 (47)	8 (36)	18 (90)
Eptifibatide >1600 ng/mL	10 (53)	14 (64)	2 (10)

Values presented as no. (%). Eptifibatide concentrations not available for 6 patients. ABW indicates actual body weight; IBW, ideal body weight.

^{*} *P*value comparing actual weight-based dosing with standard dosing = 0.48.

[†] *P*value comparing ideal body weight-based dosing with standard dosing = 0.004.

Table 4

Clinical outcomes

Clinical Outcomes	Standard Dosing (N=22)	ABW-Based Dosing (N=23)	IBW-Based Dosing (N=22)	All (N=67)
In-hospital death	0 (0)	0 (0)	1 (4.5)	1 (1.5)
Periprocedural MI	0 (0)	0 (0)	2 (9.1)	2 (3)
TIMI minor bleeding	2 (9.1)	1 (4.3)	0 (0)	3 (4.5)
TIMI major bleeding	1 (4.5)	0 (0)	0 (0)	1 (1.5)
Transfusion	1 (4.5)	0 (0)	0 (0)	1 (1.5)

Values presented as no. (%).ABW indicates actual body weight; IBW, ideal body weight; MI, myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction.