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Highlights

- Eptifibatide mediates potent antithrombotic effects when used in primary PCI
- Standard eptifibatide infusion for several hours increases bleeding complications
- A novel, short eptifibatide regimen retains ischemic protection during primary PCI
- Bleeding complications are greatly reduced by the abbreviated eptifibatide regimen
- Avoiding prolonged eptifibatide treatment may improve clinical outcomes

Efficacy and Safety of Abbreviated Eptifibatide Treatment in Patients with ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention

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Abstract

The glycoprotein IIb/IIIa inhibitor eptifibatide, administered as bolus followed by infusion, is an adjunctive antithrombotic treatment during primary percutaneous coronary intervention (PCI) in selected patients with ST-segment elevation myocardial infarction (STEMI). Whether both bolus and infusion are necessary to improve outcomes is unknown. We hypothesized that primary PCI with eptifibatide bolus only is non-inferior to the conventional treatment (bolus and infusion) with regard to infarct size, while reducing bleeding complications. We analyzed 720 consecutive STEMI patients receiving eptifibatide bolus only or conventional treatment in an observational case-control study utilizing propensity score matching of clinical and intervention-specific confounders. Infarct size was estimated based on myocardial bound creatine kinase (CK-MB), creatine kinase (CK), and CK area under the curve (CK-AUC) values, with a pre-specified non-inferiority margin of 20%. Major bleeding was defined as type 2, 3 or 5 on the Bleeding Academic Research Consortium (BARC) classification. Eptifibatide bolus only was administered to 147 patients (20%), which were matched 1:1 to patients receiving conventional treatment. Based on peak CK-MB, CK and CK-AUC values, infarct size was -8.4% (95% CI [-31.2%, 14.4%]), -11.6% (95% CI [-33.5%, 10.3%]), and -13.9% (95% CI [-34.1%, 6.2%]) after eptifibatide bolus, respectively, reaching pre-specified non-inferiority compared to conventional treatment. Bolus treatment significantly reduced major bleeding complications (OR 0.48, 95% CI [0.30, 0.79]). In conclusion, eptifibatide given as abbreviated bolus only to selected STEMI patients undergoing primary PCI was non-inferior regarding infarct size and resulted in less bleeding complications compared to conventional bolus and infusion treatment.

Keywords: Antithrombotic therapy; Glycoprotein IIb/IIIa inhibitor; Myocardial infarction; PCI

In patients with ST-segment elevation myocardial infarction (STEMI), antithrombotic therapy with aspirin, a $P2Y_{12}$ inhibitor, and heparin is essential to reduce coronary thrombus burden, and to facilitate primary percutaneous coronary intervention (PCI).[1,2] In case of periinterventional thrombotic complications, additional use of a glycoprotein IIb/IIIa inhibitor (GPI) is a reasonable bailout treatment.[1,2] Eptifibatide is a potent GPI[3] that rapidly inhibits platelet aggregation when administered as bolus followed by infusion for 18-24 hours,[4] which reduced ischemic endpoints and death in patients undergoing PCI in clinical trials performed in the 1990's.[4-6] However, GPI use has since declined with the introduction of the potent $P2Y_{12}$ inhibitors prasugrel and ticagrelor[7,8] as well as new-generation drug-eluting stents.[9,10] Mainly, concerns about GPI-related bleeding complications are no longer considered to be offset by antithrombotic benefits.[3] However, whether the eptifibatide infusion in addition to the bolus treatment is necessary to improve outcomes of STEMI patients is unknown. We conducted a matched case-control study to test the hypothesis that primary PCI with an eptifibatide bolus only is non-inferior to the conventional (bolus and infusion) treatment regarding myocardial infarct size, while reducing bleeding complications.

Methods

The cohort includes consecutive STEMI patients treated between December 1st, 2009, and April 30st, 2016, at the Triemli Hospital in Zürich, Switzerland, by a primary PCI strategy within 24 hours of symptom onset. Data were collected by the treating physicians, and checked for completeness, plausibility and consistency by a trained study nurse. Patients resuscitated from out of hospital cardiac arrest as well as patients who did not have Thrombolysis in Myocardial Infarction (TIMI) 3 coronary blood flow at the end of the PCI were ineligible. Additional pre-specified exclusion criteria were culprit lesions in the left main coronary artery or in a coronary artery bypass graft, patients who did not undergo PCI with stent implantation, and cases with missing data. Glomerular filtration rate was calculated using the Cockcroft-Gault equation.[11]

Increased bleeding risk was assumed if patients were taking oral anticoagulants (vitamin K antagonists, direct thrombin or factor Xa inhibitors), in patients with a haematocrit <30% or a thrombocyte count <80'000/μL, or if patients had undergone surgery within 6 weeks prior to primary PCI. Data acquisition and analyses have been approved by the local ethics committee (KEK-ZH-Nr. 2014-0671) and are in accordance with the World Medical Association Declaration of Helsinki and with good clinical practice guidelines. The ethics committee waived the requirement to obtain patients' informed consent.

Acute STEMI was diagnosed and treated according to the latest guidelines at presentation.[1,2] Briefly, reperfusion therapy based on a primary PCI strategy was initiated as soon as possible. For platelet inhibition, aspirin (250 or 500 mg i.v.) was administered during transfer to the catheterization laboratory, and a $P2Y_{12}$ inhibitor (prasugrel 60 mg, ticagrelor 180 mg, or clopidogrel 600 mg) was given before or at the time of PCI. In addition, patients received intravenous anticoagulant therapy with unfractionated heparin (initial bolus of 5000 U, followed by additional doses to achieve an activated clotting time of 250-300 sec). All procedural aspects during PCI such as access route, techniques involved in angioplasty including the use of thrombus aspiration and selection of coronary stents, as well as revascularization of significant coronary stenoses in addition to the infarct-related artery were at the discretion of the treating interventional cardiologist.

Eptifibatide was used in case of angiographic evidence of a large thrombus burden, or as bailout treatment for thrombotic complications such as no-reflow, distal embolization or side branch occlusion.[1,2] Eptifibatide was administered intravenously as a double bolus of 180 μg/kg given at a 10 min interval ("bolus treatment").[4] Whether eptifibatide treatment was continued with an infusion of 2.0 μg/kg/min for 8 to 10 hours ("conventional treatment") was at the choice of the interventional cardiologist.

Efficacy outcomes were related to myocardial infarct size estimated by myocardial biomarkers, which highly correlate with infarct size measured by cardiac imaging techniques, as

well as clinical outcomes (congestive heart failure and death).[12,13] Primary efficacy outcome was the peak value of the myocardial bound creatine kinase (CK-MB) isoenzyme during repeated sampling. Secondary efficacy outcomes included peak total creatine kinase (CK) and CK area under the curve (CK-AUC) values during repeated sampling, as well as ST segment resolution in the electrocardiogram within 24 hours after PCI as an indicator of microvascular coronary obstruction. The primary safety outcome was major bleeding, which was defined as type 2, 3 or 5 on the Bleeding Academic Research Consortium (BARC) classification.[14] Secondary safety outcomes included death and requirement for urgent target lesion revascularization during the index hospitalization.

All analyses were performed using R software version 3.6.1 (The R Foundation for Statistical Computing, Vienna, Austria), and R programming code will be made available upon request. Results are reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[15] To balance baseline covariates between patients receiving eptifibatide bolus only or conventional bolus and infusion treatment, propensity scores were calculated by logistic regression, and propensity score matching was performed. The following covariates were pre-selected and used for the propensity score based on perceived clinical importance: age, sex, glomerular filtration rate, previous myocardial infarction, diabetes, year of the intervention, access route (femoral or radial), location of the culprit lesion, presence of stent thrombosis, number of implanted stents, total stent length, PCI-related complications (no-reflow, distal thrombus embolization, side branch occlusion or dissection of a coronary artery), and left ventricular ejection fraction. Balance between treatment groups before and after matching was assessed by standardized mean differences, and a value ≤0.1 was accepted.[16] The effect of eptifibatide bolus only as compared to conventional bolus and infusion treatment was then determined with linear regression analyses for continuous outcome variables, and with logistic regression analyses for binary outcome variables. There was a small number of treating interventional cardiologists, which could not be used in the matching process as the treatment

decision itself was clustered within interventionalists. Therefore, we accounted for the clustering with random effects related to the interventional cardiologist. Any unbalanced baseline covariates (standardized mean difference >0.1) were also included in the models.[17] For efficacy outcomes, data were studied after logarithmic transformation and given as relative difference with 95% confidence intervals (CI). A pre-specified non-inferiority margin of 20% was chosen as clinically relevant.[18] For the primary safety outcome, odds ratio (OR) with 95% CI was calculated. Subsequently, the robustness of the results was studied in a sensitivity analysis by calculating Rosenbaum bounds.[17] In addition, single imputation was used for missing values after matching, and Rosenbaum bounds were calculated for that analysis as well.

Continuous normally distributed variables were reported as mean and standard deviation (SD), and differences between groups were compared using the unpaired Student's *t*-test. Categorical variables were analysed using the Pearson χ^2 test or the Fisher's exact test as appropriate. Corresponding p values for the comparison of baseline characteristics were considered exploratory, with a two-sided p value <0.05 indicating statistical significance.

Results

Of 2215 consecutive STEMI patients undergoing primary PCI, 147 and 516 patients receiving eptifibatide bolus only or conventional bolus and infusion treatment, respectively, were included in subsequent analyses (Figure 1). Before matching, patients receiving eptifibatide bolus only were older compared to conventionally treated patients (62.4 ± 11.7 vs 59.7 ± 11.6 years, p = 0.013), had worse glomerular filtration rate (97 ± 33 vs 105 ± 40 ml/min/m^2, p = 0.027), were treated later in the observation period and more frequently via transradial access (69% vs 39%, p <0.001), and with a longer total stent length (43.2 ± 24.3 vs 32.7 ± 21.2 mm, p <0.001). No difference with respect to other variables was observed. Clinical and intervention-related characteristics after 1:1 matching of the 147 patients receiving eptifibatide bolus only with

conventionally treated patients are shown in Tables 1 and 2. While exploratory p values showed no significance between the matched groups for any of the variables assessed, standardized mean differences indicated imbalance for age and glomerular filtration rate, which were adjusted for in subsequent regression analyses. In the conventional treatment group, the duration of the eptifibatide infusion was 514 ± 100 minutes, and 137 patients (93%) received eptifibatide for the full duration of 8 to 10 hours.

Myocardial infarct size as assessed by peak CK-MB values was similar in the eptifibatide bolus and the conventional treatment groups (204 ± 149 vs 238 ± 173 IU/L; relative difference -8.4%, 95% CI [-31.2%, 14.4%]) (Figure 2). Similarly, there was no difference between groups with regard to peak CK (2378 ± 2116 vs 2694 ± 2190 IU/L; relative difference -11.6%, 95% CI [-33.5%, 10.3%]) and CK-AUC values (10.5 ± 8.7 vs 12.2 ± 9.2 arbitrary units; relative difference -13.9%, 95% CI [-34.1%, 6.2%]). The upper limits of these variables did not cross the pre-specified non-inferiority margin of 20%,[18] establishing non-inferiority of the abbreviated bolus only compared with the conventional treatment regimen. Furthermore, there was no difference between groups with regard to ST-segment resolution in the ECG as a marker of microvascular coronary obstruction (64 ± 34 vs 61 ± 44%; relative difference 3.6%, 95% CI [-5.5%, 12.8%]).

Major bleeding complications (BARC type 2, 3 or 5[14]) occurred in 47 patients (32%) of the eptifibatide bolus and in 69 patients (47%) of the conventional treatment group (p = 0.01) (Figure 3); bleeding with a haemoglobin drop of 3-5 g/dL or requiring transfusion (BARC type 3a) was observed in 1 (0.7%) and 3 (2.0%) patients, respectively. As a result, abbreviated eptifibatide bolus only was associated with a 52% risk reduction in major bleeding complications (OR 0.48, 95% CI [0.29 to 0.79]) compared to the conventional treatment. There was no interaction with the access route (p = 0.24), as also indicated by similar bleeding risk reductions for transradial PCI (OR 0.44, 95% CI [0.22, 0.88]) and transfemoral PCI (OR 0.42, 95% CI [0.17, 1.02]) in the eptifibatide bolus as compared to the conventional treatment group. Sensitivity analyses indicated that superiority of the eptifibatide bolus treatment remained robust even if unknown confounders not considered in

the matching procedure were present (Gamma max = 1.3). When missing data were imputed once, the results were unchanged (OR 0.55, 95% CI [0.35, 0.88]) and robust up to Gamma max = 1.5.

There were 8 deaths during hospitalization (hospital mortality 2.7%), 3 in the eptifibatide bolus and 5 in the conventional treatment group. Only 1 patient (0.3%), who did receive eptifibatide bolus only, had to undergo urgent target lesion revascularization during hospitalization. These event rates are too small to conduct superiority analyses.

Discussion

The results of this matched case-control study suggest that eptifibatide treatment facilitating successful primary PCI of selected contemporary STEMI patients can be safely abbreviated to a bolus only regimen. This strategy was not inferior with regard to myocardial infarct size, and reduced the risk of post-procedural major bleeding complications by more than 50% when compared to the conventional eptifibatide bolus and infusion regimen.

Previous randomized trials have consistently shown that intensifying platelet inhibition using GPIs[19] or potent $P2Y_{12}$ inhibitors such as prasugrel[7] and ticagrelor[8] reduces ischemic complications in patients with acute coronary syndromes. While intravenous GPI administration provides fast and powerful inhibition of platelet aggregation even in the highly pro-thrombotic state encountered in STEMI patients,[3] optimal levels of platelet inhibition may take up to 4 hours after oral administration of a prasugrel or ticagrelor loading dose.[20] However, since the clinical trials investigating the efficacy of GPIs[4-6] precede the availability of the potent $P2Y_{12}$ inhibitors with greater efficacy than clopidogrel,[7,8] optimal use and bridging between these agents after successful PCI using new-generation drug-eluting stents[9,10] is uncertain. A recent small study showed similar inhibition of platelet reactivity 2 hours after eptifibatide bolus or conventional treatment with concomitant ticagrelor administration, although STEMI patients were not

investigated.[21] Furthermore, administration of prasugrel and a bolus of the GPI tirofiban yielded very high inhibition of platelet reactivity in STEMI patients that was similar compared with a tirofiban bolus and 2-hour infusion regimen.[22] These observations provided the rationale to study the clinical efficacy of an abbreviated GPI bolus only strategy in contemporary STEMI treatment.

In the present study, prasugrel or ticagrelor was administered to >90% of STEMI patients, which successfully underwent primary PCI with stent implantation yielding normal coronary blood flow. These patients did not benefit from extended eptifibatide treatment with regard to myocardial infarct size, suggesting that bridging to potent $P2Y_{12}$ inhibitors may be sufficient to retain full ischemic protection after eptifibatide bolus administration. The current findings in the highly pro-thrombotic state of STEMI extend previous observations in stable, low-risk patients, who had similar ischemic outcomes when eptifibatide was truncated to a short (<2 hours) infusion as compared to the conventional (18-24 hours) treatment after bolus administration.[23] Similarly, an observational analysis comparing eptifibatide bolus versus conventional treatment in non-emergent, stable patients found no difference in periprocedural CK-MB elevation, stent thrombosis or target lesion revascularization.[24] Thus, accumulating evidence supporting abbreviated eptifibatide regimens may help to adapt current treatment recommendations,[1,2] which are based on previous trials neither distinguishing the individual effects of the GPI bolus and the extended infusion, nor evaluating the role of GPIs in the presence of potent $P2Y_{12}$ inhibitors.[4-6]

Importantly, we observed very low rates of ischemic endpoints routinely used in previous trials such as urgent target lesion revascularization and mortality, likely reflecting recent technological advances in the care of STEMI patients. As primary outcome, we therefore chose to study CK/CK-MB values, which similar to troponin values show a high correlation with myocardial infarct size measured by cardiac imaging techniques, as well as the incidence of congestive heart failure and mortality.[12,13] In line with the comparable outcomes in biochemical infarct size, we also detected no difference between the treatment groups with regard to ECG changes indicating microvascular obstruction, which has been associated with impaired myocardial perfusion that may

be improved by GPIs due to disaggregation of already formed, often embolized platelet aggregates.[25] However, whether such treatment improves cardiovascular outcomes remains unclear when considering previous studies showing no beneficial effects of routine thrombus aspiration during primary PCI.[26,27]

Not surprisingly, abbreviated GPI regimens have consistently been associated with less major bleeding complications,[21,23,24,28] which independently predict increased mortality and adverse cardiovascular events regardless of the success of reperfusion therapy in patients with acute coronary syndromes.[29] Furthermore, both access site bleeding and systemic bleeding complications are associated with mortality that remains increased even after 1 year.[30] Independent of a transradial or transfemoral access route, we observed a substantial, more than 50% lower risk of major hemorrhage requiring diagnostic studies or specific treatment including blood transfusions when eptifibatide administration was abbreviated to bolus only. Although primary PCI represents a delicate balance between minimizing both thrombotic and bleeding complications, tailoring procedural practices such as avoiding unnecessary, prolonged GPI-mediated inhibition of platelet aggregation as shown in the present study may ultimately result in improved clinical outcomes.

We believe that our results are applicable to most STEMI patients undergoing contemporary PCI with successful stent implantation and an indication for eptifibatide treatment, provided that the angiographic result is satisfactory without complications that necessitate prolonged GPI use. Nonetheless, the main limitation of this study relates to its observational design. We used propensity score matching based on multiple variables describing individual patients as well as potentially influencing treatment outcomes, a method widely used to imitate a randomized study. In addition, sensitivity analyses verified the robustness of the data. However, we cannot exclude that the results may have still been affected by unmeasured confounders leading to a biased estimate of the treatment effect. On the other hand, observational data from a contemporary, unselected cohort more likely provides an indication of what is achieved in routine

clinical practice than a randomized trial. Although comparable to previous studies, the sample size of patients receiving eptifibatide as abbreviated regimen may be insufficient to detect small difference in rare events, such as stent thrombosis. Furthermore, we only report implications of eptifibatide treatment regimens on hospital outcomes, but not on intermediate or long-term follow-up. We also did not quantify myocardial infarct size by cardiac imaging techniques, given that these measurements show a high correlation with CK/CK-MB values.[12,13]

In conclusion, we found that eptifibatide bolus only was non-inferior regarding infarct size and reduced the risk of post-procedural major bleeding complications by more than 50% compared to conventional bolus and infusion treatment of selected STEMI patients undergoing successful primary PCI. Such abbreviated eptifibatide treatment may provide full inhibition of platelet activity at the time of PCI while allowing bridging to potent $P2Y_{12}$ inhibition, thus representing an appealing strategy to retain the ischemic protection of GPIs while improving their safety profile.

CRediT Author Statement

Florian Fischer: Investigation, Writing – Review & Editing. **Samriddhi Buxy:** Formal analysis, Validation, Writing – Review & Editing. **David J. Kurz:** Conceptualization, Writing – Review & Editing. **Franz R. Eberli:** Writing – Review & Editing, Funding acquisition. **Oliver Senn:** Writing – Review & Editing, Supervision. **Rainer Zbinden:** Conceptualization, Writing – Review & Editing. **Ulrike Held:** Formal analysis, Validation, Writing – Review & Editing, Supervision. **Matthias R. Meyer:** Conceptualization, Methodology, Writing – Original Draft, Supervision, Funding acquisition.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Figure legends

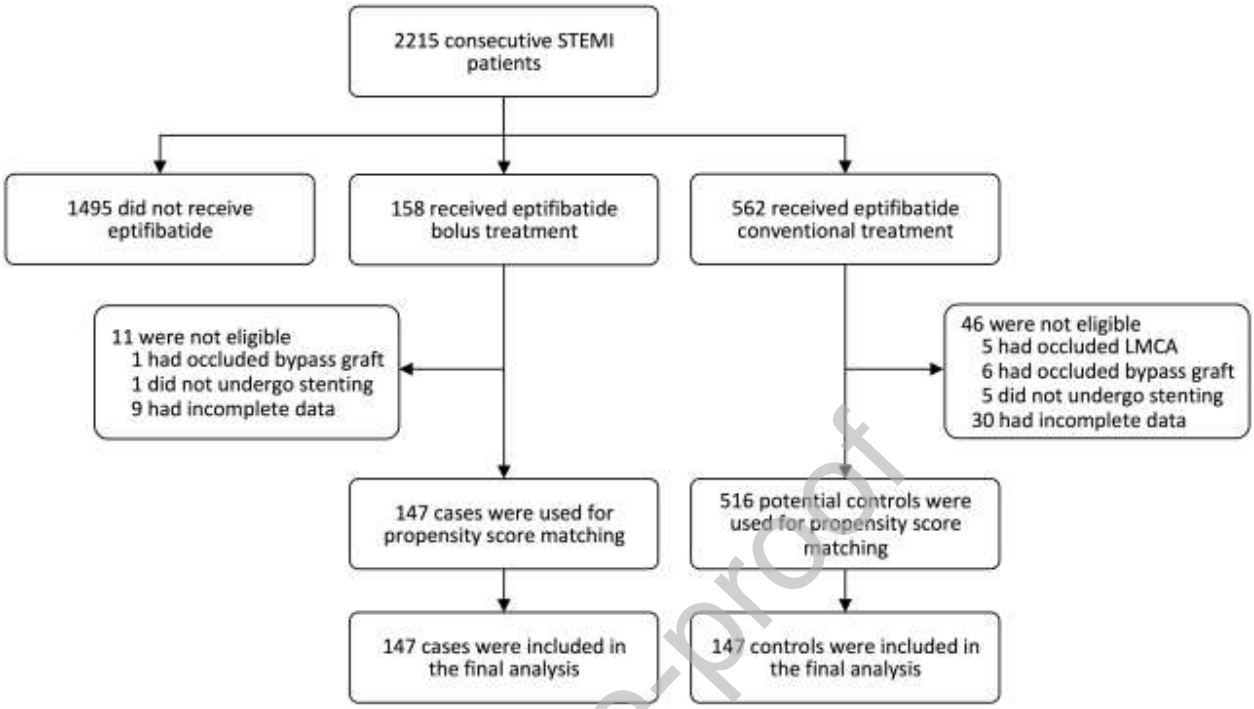

Figure 1. Flow diagram of treatment-related patient groups before and after propensity score matching. LMCA = left main coronary artery; STEMI = ST-segment elevation myocardial infarction.

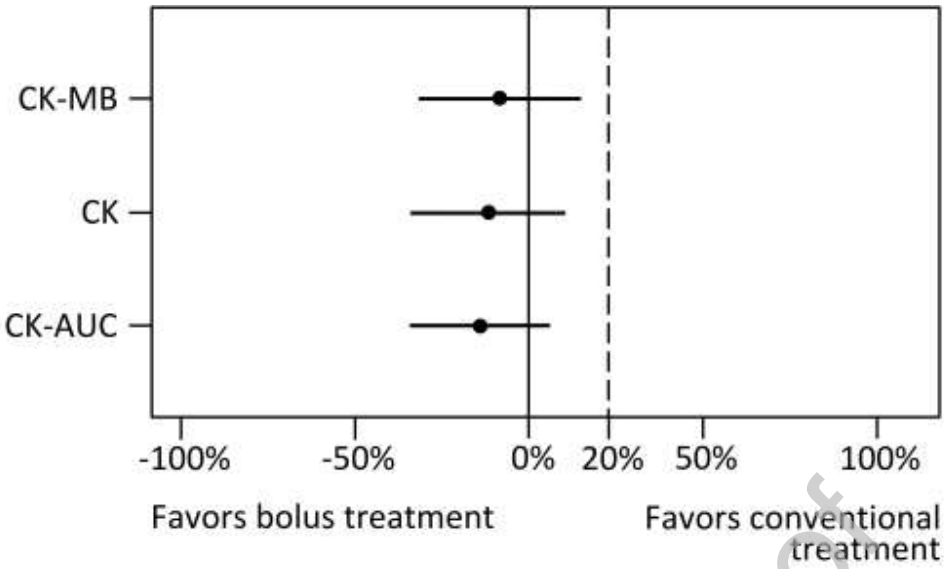

Figure 2. Efficacy outcomes of primary percutaneous coronary intervention facilitated by abbreviated bolus or conventional eptifibatide treatment. Error bars indicate 95% confidence intervals. For the abbreviated bolus treatment, a pre-specified non-inferiority margin of 20% (dashed line) was selected as clinically relevant.[18] CK = peak total creatine kinase; CK-AUC = creatine kinase area under the curve; CK-MB = peak myocardial bound creatine kinase.

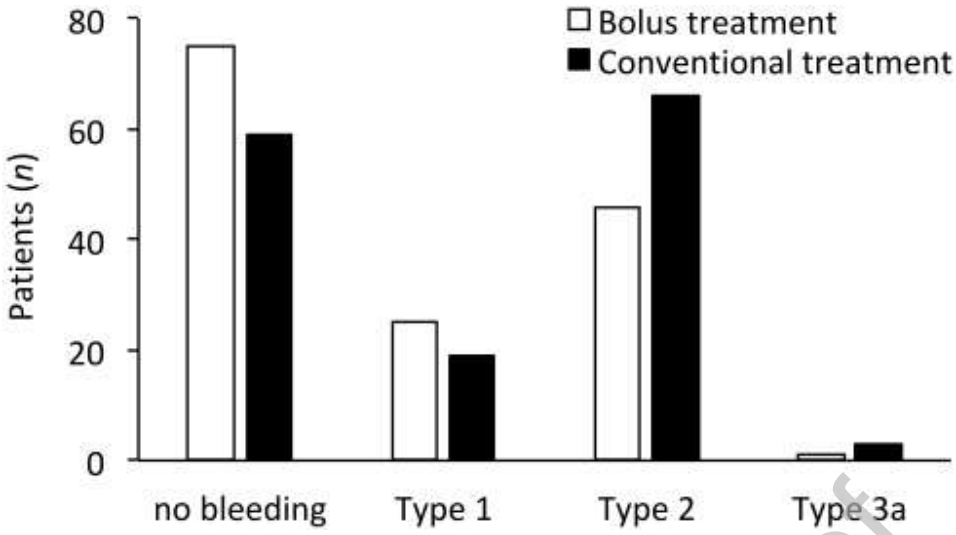

Figure 3. Bleeding complications after primary percutaneous coronary intervention facilitated by abbreviated bolus or conventional eptifibatide treatment. Bleeding complications are defined according to the Bleeding Academic Research Consortium (BARC) scale,[14] with type 1 indicating bleeding that is not actionable; type 2, clinically overt hemorrhage requiring diagnostic studies, hospitalization or treatment; type 3a, bleeding with a haemoglobin drop of 3-5 g/dL or requiring transfusion.

Table 1. Clinical characteristics after propensity score matching of the study patients.

Variable	Bolus treatment (n = 147)	Conventional treatment (n = 147)	p Value	SMD
Age (years), mean ± SD	62.4 ± 11.3	60.5 ± 10.5	0.13	0.172
Women	35 (24%)	28 (19%)	0.39	0.048
Hypertension	66 (45%)	68 (46%)	0.91	0.014
Diabetes mellitus	22 (15%)	26 (18%)	0.64	0.027
Dyslipidemia	102 (69%)	104 (71%)	0.90	0.014
Smoker	61 (42%)	65 (44%)	0.72	0.027
Family history of coronary artery disease	37 (25%)	49 (33%)	0.16	0.082
Previous myocardial infarction	30 (20%)	25 (17%)	0.55	0.034
Previous percutaneous coronary intervention	30 (20%)	24 (16%)	0.45	0.041
Previous coronary artery bypass grafting	2 (1%)	0	0.48	0.014
Previous stroke	3 (2%)	3 (2%)	1.00	0.000
Body mass index (kg/m^2), mean ± SD	27.3 ± 4.7	26.9 ± 3.8	0.35	0.098
Glomerular filtration rate ($ml/min/m^2$)*, mean ± SD	97 ± 33	103 ± 40	0.19	0.170
Killip class ≥3	10 (7%)	6 (4%)	0.44	0.027
Increased bleeding risk†	6 (4%)	2 (1%)	0.28	0.027

* Estimated by the Cockcroft-Gault equation.[11]

† Assumed if a hematocrit <30% or a thrombocyte count <80'000/μL was measured, if patients were taking oral anticoagulants or had undergone surgery within 6 weeks prior to primary PCI.

SD = standard deviation; SMD = standardized mean difference.

Table 2. Intervention-related characteristics after propensity score matching of the study patients.

Variable	Bolus treatment (n = 147)	Conventional treatment (n = 147)	p Value	SMD
Access route (radial)	101 (69%)	106 (72%)	0.61	0.034
Sheath size (French), mean ± SD	6.02 ± 0.18	6.01 ± 0.12	0.71	0.037
Coronary culprit narrowing			0.96	
Proximal left anterior descending	37 (25%)	37 (25%)		0.000
Mid or distal left anterior descending	25 (17%)	22 (15%)		0.020
Proximal left circumflex / right	33 (22%)	36 (25%)		0.020
Mid or distal left circumflex / right	52 (35%)	52 (35%)		0.000
Bifurcation lesion	19 (13%)	16 (11%)	0.72	0.020
Stent thrombosis	17 (12%)	16 (11%)	1.00	0.007
Left ventricular ejection fraction (%), mean ± SD	51 ± 12	52 ± 11	0.63	0.053
Total stent length (mm), mean ± SD	43.2 ± 24.3	42.7 ± 26.0	0.86	0.021
Number of stents ≥3	35 (24%)	35 (24%)	1.00	0.000
PCI-related complication*	13 (9%)	15 (10%)	0.84	0.014
Aspirin before PCI	143 (97%)	138 (94%)	0.09	0.041
Aspirin after PCI	147 (100%)	146 (99%)	1.00	0.014

Heparin before PCI	146 (99%)	145 (99%)	0.61	0.007
Heparin after PCI	25 (17%)	17 (12%)	0.24	0.006
$P2Y_{12}$ inhibitor before PCI			0.68	
Prasugrel	20 (14%)	13 (9%)		0.054
Ticagrelor	13 (9%)	14 (10%)		0.057
Clopidogrel	13 (9%)	11 (8%)		0.054
$P2Y_{12}$ inhibitor after PCI			0.40	
Prasugrel	101 (69%)	111 (76%)		0.068
Ticagrelor	30 (20%)	25 (17%)		0.034
Clopidogrel	16 (11%)	11 (8%)		0.034

* Including no-reflow, distal thrombus embolization, side branch occlusion or dissection of a coronary artery.

PCI = percutaneous coronary intervention; SD = standard deviation; SMD = standardized mean difference.