Comparison of In-Hospital Bleeding and Cardiovascular Events with High-Dose Bolus Tirofiban and Shortened Infusion to Short-Duration Eptifibatide as Adjunctive Therapy for Percutaneous Coronary Intervention

Gabrielle L. Anderson, PharmD[a,*], Jennifer L. Osborn, PharmD[a], Scott D. Nei, PharmD[a], Malcolm R. Bell, MD[b], Gregory W. Barsness, MD[b], Kristin C. Mara, MS[c], and Narith N. Ou, PharmD[a]

Potent platelet inhibition is one of the most important medical interventions to prevent ischemic complications during and after percutaneous coronary intervention (PCI). Practice has evolved with the introduction of potent oral $P2Y_{12}$ inhibitors that provide quick, effective platelet inhibition, and the need for routine glycoprotein IIb/IIIa inhibitors (GPIs) has decreased. Additionally, a shorter duration of GPI infusion has been shown to be safe with adequate oral antiplatelet loading, but clinical outcome data are limited to eptifibatide. This single-center, retrospective cohort study analyzed in-hospital outcomes for patients who received adjunctive GPI therapy for PCI before and after an institution-wide switch to high-dose bolus tirofiban with shortened infusion from short-duration eptifibatide. The primary end point was a composite in-hospital outcome of major and minor bleeding and cardiovascular events (death, myocardial infarction, coronary artery bypass grafting, ischemic stroke, and target vessel revascularization). Secondary end points included bleeding and cardiovascular event types. A total of 357 and 446 patients received eptifibatide and tirofiban, respectively, from February 1, 2014 through September 30, 2017. Thirty five eptifibatide and 46 tirofiban patients experienced an in-hospital composite event (9.8% vs 10.3%, $p = 0.81$). There was no difference found between in-hospital bleeding (6.4% vs 5.4%, $p = 0.52$) or cardiovascular events (5.6% vs 6.5%, $p = 0.60$) with the use of eptifibatide or tirofiban, respectively. Multivariable analysis showed that patients with transradial access or an indication of unstable angina were less likely to experience an in-hospital composite event (OR 0.30 and 0.19, respectively, $p < 0.001$ for both). In conclusion, the use of high-dose bolus tirofiban with shortened infusion versus short-duration eptifibatide was not associated with an increase of in-hospital bleeding or cardiovascular events. **(Am J Cardiol 2019;123:44−49)**

The use of potent oral $P2Y_{12}$ inhibitor loading is the standard of care for patients undergoing percutaneous coronary intervention (PCI) to reduce major adverse cardiac events.[1,2] Oral $P2Y_{12}$ inhibitors may have notable clinical limitations including delayed onset and offset of action, variable absorption, and possible inadequate platelet inhibition at the time of PCI.[3−5] Additional antiplatelet therapy, with an adjunctive glycoprotein IIb/IIIa inhibitor (GPI) such as eptifibatide or tirofiban, may be required in certain instances. Despite the favorable pharmacokinetic and pharmacodynamic properties of GPIs, bleeding risk remains a major concern with their use.[4] In approval trials, both eptifibatide and tirofiban were infused for around 18 to 24 hours after bolus dosing.[6−14] Until recently, eptifibatide was more commonly used over tirofiban, but in October 2013 the FDA approved a new high-dose bolus (HDB) dosing strategy for tirofiban, which was shown to be similarly effective to eptifibatide and was marketed at a reduced cost leading to increased uptake in many hospitals.[15,16] With oral $P2Y_{12}$ inhibitors achieving adequate platelet inhibition within 6 hours of a load, the duration of GPI use can be shortened to bridge to the peak effect of these agents, however, optimal duration is unknown.[6−8,17] The purpose of this study was to assess whether a shortened infusion of tirofiban can provide similar outcomes as short-duration eptifibatide, as this comparison has not been previously reported in the literature.

Methods

A retrospective cohort study was conducted using electronic medical record data from all patients who underwent

[a]Department of Pharmacy Services, Mayo Clinic, Rochester, Minnesota; [b]Department of Cardiovascular Medicine, Mayo Clinic, Rochester, Minnesota; and [c]Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, Minnesota. Manuscript received August 2, 2018; revised manuscript received and accepted September 18, 2018.

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*Corresponding author: Tel: 1-507-255-6099; fax: 1-507-255-7556.

E-mail address: anderson.gabrielle@mayo.edu (G.L. Anderson).

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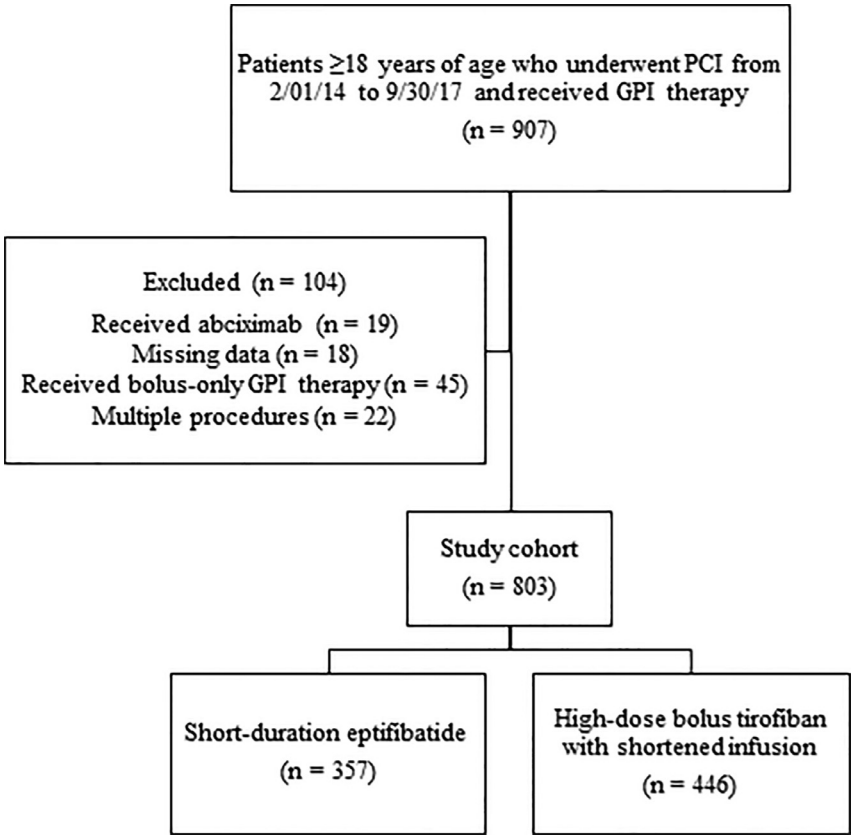

Figure 1. Study design.

PCI and received adjunctive GPI therapy from February 1, 2014 through September 30, 2017 at Mayo Clinic Hospital – Rochester. The study was reviewed and approved by the Mayo Clinic Institutional Review Board. All patients received eptifibatide from February 1, 2014 through January 31, 2016 before the switch to tirofiban starting February 1, 2016 through September 30, 2017. During the study period, 907 patients received GPI as adjunctive therapy for PCI (Figure 1). Eighty two patients were excluded; 19 received abciximab, 18 had missing data, and 45 received bolus-only GPI therapy. Additionally, 22 patients underwent multiple procedures for which only the first procedure was included in the final analysis.

As of February 1, 2016, the hospital switched from short-duration eptifibatide (180 mcg/kg × 2 doses followed by a 2 mcg/kg/min IV infusion to complete a 75 mg/100 ml vial) to HDB tirofiban with shortened infusion (25 mcg/kg intravenous (IV) bolus followed by a 0.15 mcg/kg/min IV infusion to complete a 5 mg/100 ml bag). The eptifibatide infusion dose was reduced to 1 mcg/kg/min in patients with a creatinine clearance <50 ml/min, whereas the tirofiban infusion dose was reduced to 0.075 mcg/kg/min in patients with a creatinine clearance ≤ 60 ml/min.[7,8] In addition to GPI therapy, patients received IV anticoagulant, aspirin, and an oral $P2Y_{12}$ inhibitor per standardized protocol.

The primary end point was a composite in-hospital outcome of bleeding events (major and minor) and cardiovascular events (death, myocardial infarction [MI], coronary artery bypass grafting, ischemic stroke, and target vessel revascularization). Secondary end points included bleeding and cardiovascular event types. All baseline and clinical data were extracted from a PCI data registry, a cardiovascular database, and electronic medical records. All cardiovascular events were reviewed and confirmed by an interventional cardiologist.

Major bleeding included central nervous system, retroperitoneal, and gastrointestinal bleeds or the requirement of transfusion of a minimum of 1 unit of red blood cells during hospitalization. Minor bleeding included hematomas or vascular access site bleeds. In-hospital death was defined as death from a cardiac cause, and MI was classified by guideline definitions.[1,2] Target vessel revascularization was defined as urgent intervention of the same lesion in the same hospitalization.

Continuous data were summarized with median and interquartile range (IQR) or mean and standard deviation (SD). Counts and percentages were used for categorical data. The Wilcoxon rank sum tests or *t* Tests and the chi-square or Fisher's exact test were used to compare continuous and categorical data, respectively, across groups. A multivariable logistic regression model was used to assess the association between regimen group and having an in-hospital bleeding or cardiovascular event after adjusting for baseline characteristics. These baseline characteristics included hypertension, previous MI, diabetes mellitus, current tobacco use, transradial access, ticagrelor administration, and unstable angina PCI indication. We estimated an overall event rate of 8%, which required 420 patients per group to detect a hazard ratio of 2 with 80% power using a 2-sided, $\alpha = 0.05$ test.[16,18,19] All tests were 2-sided, and a p

Table 1
Baseline demographics and characteristics

Variable	Eptifibatide (n = 357)	Tirofiban (n = 446)	p Value
Age, mean (SD), (years)	64.7 (13.3)	67.4 (12.6)	0.005
Male	270 (75.6%)	339 (76.0%)	0.90
White	343 (96.1%)	414 (92.8%)	0.049
Weight, median (IQR), (kg)	89.7 (77.1−100.0)	91.0 (77.0−106.0)	0.24
Pre-PCI serum creatinine, median (IQR), (mg/dl)	1.0 (0.8−1.2)	1.0 (0.8−1.2)	> 0.99
Creatinine clearance, median (IQR), (ml/min)	89.8 (65.5−117.9)	89.4 (60.9−117.4)	0.65
Pre-PCI hemoglobin, median (IQR), (g/dl)	14.1 (12.9−15.1)	13.9 (12.6−15.1)	0.34
Pre-PCI platelet count, median (IQR), ($\times 10^9$/L)	223.0 (187.0−263.0)	218.5 (179.0−258.0)	0.29
Time from PCI to hospital discharge, median (IQR), (days)	2.0 (1.0−3.0)	2.0 (1.0−3.0)	0.35
Glycoprotein IIb/IIIa inhibitor duration, median (IQR), (hours)	2.9 (0.9−7.4)	3.8 (2.7−7.0)	< 0.001
Hypertension	154 (43.1%)	329 (73.8%)	< 0.001
Coronary artery disease*	61 (17.1%)	132 (29.6%)	< 0.001
Myocardial infarction (> 7 days earlier)	35 (9.8%)	94 (21.1%)	< 0.001
Percutaneous coronary intervention	39 (10.9%)	107 (24.0%)	< 0.001
Coronary artery bypass grafting	12 (3.4%)	45 (10.1%)	< 0.001
Cerebral vascular attack or transient ischemic attack	25 (7.0%)	50 (11.2%)	0.042
Left ventricular ejection fraction ≤ 40%†	28 (7.8%)	42 (9.4%)	0.61
Diabetes mellitus	50 (14.0%)	136 (30.5%)	< 0.001
Current smoker	43 (12.0%)	101 (22.6%)	< 0.001
Tumor/lymphoma/leukemia	22 (6.2%)	45 (10.1%)	0.074
Vascular access			
Transradial	200 (56.0%)	298 (66.8%)	0.002
Transfemoral	157 (44.0%)	147 (33.0%)	0.001
Other procedural medications			
Unfractionated heparin	354 (99.2%)	443 (99.3%)	0.78
Aspirin	348 (97.5%)	438 (98.2%)	0.61
Bivalirudin	3 (0.8%)	2 (0.4%)	0.48
Clopidogrel	211 (59.1%)	245 (54.9%)	0.12
Prasugrel	2 (0.6%)	1 (0.2%)	0.33
Ticagrelor	136 (38.1%)	190 (42.6%)	0.075
Indication for percutaneous coronary intervention			0.002
ST-elevation myocardial infarction	160 (44.8%)	180 (40.4%)	
Non-ST-elevation myocardial infarction	64 (17.9%)	97 (21.7%)	
Unstable angina pectoris	104 (29.1%)	98 (22.0%)	
Stable angina pectoris	14 (3.9%)	35 (7.8%)	
Other‡	15 (4.2%)	36 (8.1%)	
Percutaneous coronary intervention			
Stent placement	332 (93.0%)	431 (96.6%)	0.019
Number of stents placed, mean (SD)	1.6 (0.9)	1.6 (0.8)	0.47
Bare-metal stent	31 (8.7%)	7 (1.6%)	< 0.001
Drug-eluting stent	302 (84.6%)	425 (95.3%)	< 0.001
Location of stent placement			
Left anterior descending artery	167 (46.8%)	213 (47.8%)	0.78
Left circumflex artery	92 (25.8%)	111 (24.9%)	0.78
Left main coronary artery	13 (3.6%)	15 (3.4%)	0.83
Right coronary artery	148 (41.5%)	181 (40.6%)	0.80

* Coronary artery disease defined per NCDR® CathPCI Registry® v4.4 Coder's Data Dictionary.
† Left ventricular ejection fraction unknown for 222 eptifibatide patients and 264 tirofiban patients.
‡ Symptoms unlikely to be ischemic or lack of symptoms.

value of ≤ 0.05 was considered statistically significant. All analyses were performed with SAS version 9.4 software (SAS Institute, Cary, North Carolina).

Results

A total of 803 patients from February 1, 2014 through September 30, 2017 were included for analysis with 357 in the short-duration eptifibatide group and 446 in the HDB tirofiban with shortened infusion group. The median GPI infusion duration was 2.9 (IQR 0.9, 7.4) and 3.8 (IQR 2.7, 7.0) hours for eptifibatide and tirofiban, respectively ($p < 0.001$). Conversion from short-duration eptifibatide (2018 average wholesale price $652.86; 75 mg) to shortened infusion tirofiban (2018 average wholesale price $296.75; 5 mg) would yield an average difference of $356.11 per patient.

At baseline, patients in the tirofiban group were older and had a higher percentage of nonwhite patients than the eptifibatide group. Patients in the tirofiban group also had

Table 2
Primary and secondary end points: composite and individual in-hospital bleeding and cardiovascular events

Outcome	Eptifibatide (n = 357)	Tirofiban (n = 446)	p Value
Composite in-hospital bleeding and cardiovascular events	35 (9.8%)	46 (10.3%)	0.81
Composite in-hospital bleeding events	23 (6.4%)	24 (5.4%)	0.52
Major bleed	15 (4.2%)	19 (4.3%)	0.97
Central nervous system	0 (0.0%)	0 (0.0%)	-
Retroperitoneal	3 (0.8%)	1 (0.2%)	0.33
Gastrointestinal	4 (1.1%)	7 (1.6%)	0.76
Blood transfusion required	10 (2.8%)	13 (2.9%)	0.92
Minor bleed	8 (2.2%)	5 (1.1%)	0.21
Composite in-hospital cardiovascular events	20 (5.6%)	29 (6.5%)	0.60
Death	12 (3.4%)	18 (4.0%)	0.62
Myocardial infarction	2 (0.6%)	4 (0.9%)	0.58
Coronary artery bypass grafting	2 (0.6%)	5 (1.1%)	0.40
Ischemic stroke	2 (0.6%)	1 (0.2%)	0.59
Target vessel revascularization	2 (0.6%)	1 (0.2%)	0.59

more co-morbidities than the eptifibatide patients, including a higher incidence of hypertension; coronary artery disease; previous MI, PCI, and/or coronary artery bypass grafting; previous cerebral vascular attack or transient ischemic attack; diabetes mellitus; and current tobacco use (Table 1).

The primary end point occurred in 35 eptifibatide and 46 tirofiban patients (9.8% vs 10.3%, p = 0.81) (Table 2). In-hospital bleeding events occurred in 23 eptifibatide and 24 tirofiban patients (6.4% vs 5.4%, p = 0.52). Of all bleeding events, 15 eptifibatide and 19 tirofiban patients experienced a major bleed (4.2% vs 4.3%, p = 0.97), whereas 8 eptifibatide and 5 tirofiban patients experienced a minor bleed (2.2% vs 1.1%, p = 0.21). In-hospital cardiovascular events occurred in 20 eptifibatide and 29 tirofiban patients (5.6% vs 6.5%, p = 0.60) (Table 2). No statistically significant difference in composite or individual rates of in-hospital bleeding and cardiovascular events was noted between the groups. Multivariable analysis showed that patients with transradial access or an indication of unstable angina were less likely to experience an in-hospital composite event (odds ratio [OR] 0.30, 95% confidence interval 0.19 to 0.50, p < 0.001 and OR 0.19, 95% confidence interval 0.08 to 0.48, p < 0.001, respectively) (Table 3).

Discussion

To our knowledge, this is the first and largest study to date to compare HDB tirofiban with shortened infusion to short-duration eptifibatide as adjunctive therapy in patients having PCI. With the increasing utilization of tirofiban in the United States versus eptifibatide along with shortened infusion dosing strategies, our goal was to provide evidence and support for the use of short infusion tirofiban as adjunctive therapy for PCI, specifically noting the incidence of in-hospital bleeding and cardiovascular events. Bleeding events were included in the primary end point due to the association with an increased risk of short- and long-term morbidity and mortality along with findings in previous studies that suggest a survival benefit from a reduction in bleeding alone.[19] The results from our cohort study did not reveal an associated increase of in-hospital bleeding or cardiovascular events with the use of HDB tirofiban with shortened infusion versus short-duration eptifibatide (9.8% vs 10.3%, p = 0.81).

Table 3
Multivariable model for composite in-hospital bleeding and cardiovascular events

Variable	Odds Ratio (95% CI)	p Value
Hypertension	0.86 (0.48−1.54)	0.61
Myocardial infarction (> 7 days earlier)	1.06 (0.53−2.14)	0.86
Diabetes mellitus	1.76 (0.98−3.16)	0.059
Current smoker	0.74 (0.37−1.48)	0.39
Transradial access	0.30 (0.19−0.50)	< 0.001
Ticagrelor use	1.58 (0.96−2.60)	0.074
Unstable angina pectoris	0.19 (0.08−0.48)	< 0.001
Group		
Tirofiban	1.01 (0.59−1.72)	0.98
Eptifibatide	Reference	-

Tirofiban, when given as a HDB followed by a full infusion, has previously been shown to be effective as adjunctive therapy in patients who underwent PCI by providing increased protection against adverse cardiac events with no significant increase in bleeding events when compared with placebo and other GPIs.[20−24] Schiariti et al conducted the first head-to-head trial to compare high-dose tirofiban versus double-bolus eptifibatide. The study included 666 patients on a single oral antiplatelet regimen undergoing PCI with a primary end point of incidence of composite ischemic events within 1 year. Overall, there were 65 composite ischemic events: 47 in the tirofiban group and 18 in the eptifibatide group (9.1% vs 12.2%, p = 0.22). The study investigators concluded that eptifibatide had a higher incidence of composite ischemic events within 1 year, which was thought to be attributed to a lower effect of eptifibatide on creatine kinase-myocardial band.[20] Although the study conducted by Schiariti et al provided a head-to-head comparison of high-dose tirofiban versus double-bolus eptifibatide, our study is unique in that the infusion duration of these agents was shortened to the completion of a single vial or bag (median infusion duration of 2.9 hours for eptifibatide and 3.8 hours for tirofiban) versus a full 18- to 24-hour infusion. Utilizing a shortened infusion has been shown to offer cost savings compared with a prolonged infusion, yet still provides adequate bridging to the onset of action of oral antiplatelet agents.[18] The shorter infusion

durations utilized in our study did not result in a significant difference in composite ischemic events, suggesting that shortened GPI infusions are an effective alternative to longer-duration GPI infusions.[18]

The multivariable model used to adjust for differences in baseline characteristics revealed that use of transradial access or a PCI indication of unstable angina was associated with a lower likelihood of experiencing an in-hospital composite event (OR 0.30 and 0.19). This finding is consistent with previous literature assessing bleeding and cardiovascular outcomes in patients with transradial versus transfemoral access and in those receiving PCI for unstable angina versus ST-elevation myocardial infarction.[24,25] Our study results build upon previous findings of the efficacy and safety of GPIs as adjunctive therapy for PCI and show that utilization of shortened infusion dosing strategies may be a reasonable option in order to minimize potential adverse side effects whereas still producing optimal patient outcomes.[26]

Our results are limited to the available data and outcomes from the PCI data registry; however, information included has been validated, and all events were reviewed and confirmed by an interventional cardiologist. Second, our sample size was limited by the number of patients who received tirofiban since the institutional-wide transition, and this ultimately impacted our power. Although we lacked power to detect statistically significant differences in our primary outcome, this is still the largest number of patients evaluated to date comparing these 2 dosing regimens, and the number of overall events found was small and does not represent a significant clinical difference. Practice and provider selection bias could have been present throughout the study period, and temporal changes in clinical practice could have occurred due to the time-based nature of the study. This could provide an explanation for some of the differences seen in patient baseline characteristics; however, we attempted to account for these differences in our multivariate analysis.

In conclusion, the transition from short-duration eptifibatide to HDB tirofiban with shortened infusion was not associated with an increase in in-hospital bleeding and cardiovascular events. HDB tirofiban with shortened infusion can be considered as an alternative to short-duration eptifibatide as adjunctive therapy for PCI.

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Disclosures

The authors have no conflicts of interest to disclose.

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