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ACUTE CORONARY SYNDROME

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The comparative safety of abciximab versus eptifibatide in patients on dialysis undergoing percutaneous coronary intervention: Insights from the Blue Cross Blue Shield of Michigan Cardiovascular Consortium (BMC2)

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Objectives: We sought to evaluate the patterns of use and outcomes associated with eptifibatide and abciximab administration among dialysis patients who underwent percutaneous coronary intervention (PCI).

Background: Contraindicated medications are frequently administered to dialysis patients undergoing PCI often resulting in adverse outcomes. Eptifibatide is a glycoprotein IIb/IIIa inhibitor that is often used during PCI and is contraindicated in dialysis.

Methods: We included dialysis patients who underwent PCI from January 2010 to September 2015 at 47 hospitals in Michigan. We compared outcomes between patients who received eptifibatide compared with abciximab. Both groups required concurrent treatment with unfractionated heparin only. In-hospital outcomes included repeat PCI, bleeding, major bleeding, need for transfusion, and death. Optimal full matching was used to adjust for non-random drug administration.

Results: Of 177 963 patients who underwent PCI, 4303 (2.4%) were on dialysis. Among those, 384 (8.9%) received eptifibatide and 100 (2.3%) received abciximab. Prior to matching, patients who received eptifibatide had higher pre-procedural hemoglobin levels (11.3 g/dL vs. 10.7 g/dL; $P < 0.001$) and less frequently had a history of myocardial infarction (36.5% vs. 52.0%; $P = 0.005$). After matching, there were no significant differences in in-hospital outcomes between eptifibatide and abciximab including transfusion (aOR: 1.15; 95%CI: 0.55-2.40; $P = 0.70$), bleeding (1.47; 0.64-3.40; $P = 0.36$), major bleeding (4.68; 0.42-52.3; $P = 0.21$), repeat PCI (0.38; 0.03-4.23; $P = 0.43$), and death (1.53; 0.2-9.05; $P = 0.64$).

Conclusions: Despite being contraindicated in dialysis, eptifibatide was used approximately 3.5 times more frequently than abciximab among dialysis patients undergoing PCI but was associated with similar in-hospital outcomes.

KEYWORDS
bleeding, dialysis, glycoprotein inhibitors, outcomes, PCI, transfusion

Abbreviations: aOR, adjusted odds ratio; ASD, absolute standardized difference; BMC2, Blue Cross Blue Shield of Michigan Cardiovascular Consortium; CAD, coronary artery disease; GPI, glycoprotein IIb/IIIa inhibitor; IABP, intra-aortic balloon pump; NCDR, National Cardiovascular Data Registry; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction; UFH, unfractionated heparin.

1 | INTRODUCTION

Due to the high prevalence of cardiovascular disease among patients with kidney disease,[1] this population frequently undergoes cardiovascular procedures such as percutaneous coronary intervention (PCI) where they are at an increased risk of post-procedural bleeding and

death compared with patients without kidney disease.[2–6] Paradoxically, patients on dialysis are also at an increased risk of thrombosis.[7] Therefore, research devoted to defining the optimal antithrombotic regimen during PCI in this population is needed. Unfortunately, due to the under-representation or exclusion of patients with kidney disease from cardiovascular randomized clinical trials,[8] there remains a remarkable dearth of evidence guiding treatment in this population.

Further complicating this issue is the fact that many medications are metabolized and excreted by the kidney, thereby placing these patients at risk of receiving contraindicated medications.[9–11] One such drug is eptifibatide—a glycoprotein IIb/IIIa inhibitor (GPI) that has been shown to reduce ischemic complications during and after PCI.[12,13] Per the manufacturer's labeling, eptifibatide is contraindicated in dialysis as its "safety and efficacy" has not been established in these patients.[14] In a landmark paper by Tsai et al,[9] the authors demonstrated that nearly a quarter of dialysis patients undergoing PCI received eptifibatide or low molecular weight heparin, two contraindicated medications in dialysis. Furthermore, they found that administration of contraindicated medications was associated with an increased risk of in-hospital major bleeding.[9]

Due to this important and alarming statistic, most would agree that efforts should be made to reduce the use of contraindicated medications during PCI in patients on dialysis. As such, we sought to evaluate the contemporary use of eptifibatide in dialysis patients undergoing PCI, and to assess the comparative safety of eptifibatide compared with abciximab in these patients using a multicenter registry in the state of Michigan.

2 | METHODS

2.1 | Study population

We performed a retrospective analysis on data from the Blue Cross Blue Shield of Michigan Cardiovascular Consortium (BMC2), a quality improvement group and regional registry of all patients undergoing PCI in the state of Michigan. A more detailed description of the registry, including data collection and auditing practices, has been described previously.[15,16] This is a prospective, multicenter, statewide registry of patients undergoing PCI at all non-federal hospitals in Michigan. For the current study, consecutive patients undergoing PCI between January 2010 and September 2015 at 47 hospitals were included.

2.2 | Study groups

We divided patients into two groups by the use of renal dialysis. Patients were considered to require dialysis if they were "undergoing either hemodialysis or peritoneal dialysis on an ongoing basis as a result of renal failure" prior to PCI.[17] To compare the safety of abciximab and eptifibatide, we stratified dialysis patients by these two drugs. Next, we excluded patients who received a GPI with any anticoagulant other than unfractionated heparin (UFH) to reduce bias associated with differential anticoagulant administration. Patients receiving low molecular weight heparin or fondaparinux were excluded because low molecular weight heparin is contraindicated in dialysis and fondaparinux is rarely used during PCI. We excluded patients who received bivalirudin and a GPI because GPIs are frequently administered with bivalirudin as a "bailout" strategy for the treatment of suboptimal procedural results or complications, thereby representing a high-risk subgroup of patients.[18] Finally, patients who underwent PCI without recorded femoral or radial access were also excluded.

2.3 | Clinical outcomes

All outcomes were measured during the incident hospitalization when PCI was performed. In-hospital outcomes included the need for transfusion, bleeding, presumed major bleeding, repeat PCI, and mortality due to any cause. The need for transfusion was defined as the receipt of ≥1 unit of red blood cell or whole blood transfusion after PCI. Bleeding, as defined by the National Cardiovascular Data Registry (NCDR), included an event within 72 h of PCI that was associated with any of the following: a drop in hemoglobin ≥3 g/dL; transfusion of whole blood or packed red blood cells; an intervention or surgery at the site of bleeding to reverse, stop, or correct the bleeding.[17] Presumed major bleeding was defined as a drop in hemoglobin >5 g/dL. Repeat PCI was defined as repeat intervention during the incident hospitalization on the lesion that was initially treated.

2.4 | Statistical analysis

Propensity scores were estimated using logistic regression models adjusting for baseline demographic and patient clinical variables (Supplemental Table S1). Using optimal full matching methods, we created matched patient strata of patients who were generally similar in terms of baseline characteristics. These strata contained varying numbers of patients with (cases) and without (controls) the covariate of interest (abciximab or eptifibatide).[19] Optimal full matching allows treatment group members to share control group members resulting in the use of many more subjects than would be the case if pairwise or "greedy" matching were used.[19] We required exact matching on race (white vs. non-white), coronary artery disease (CAD) presentation (ST-segment elevation myocardial infarction [STEMI], non-ST-segment elevation myocardial infarction [NSTEMI], unstable angina, stable angina, or other), cardiogenic shock within 24 h prior to or at the start of PCI, prior coronary artery bypass grafting, pre-procedural cardiac arrest, and use of an intra-aortic balloon pump (IABP) or other mechanical ventricular support devices. Absolute standardized differences (ASDs) were estimated for each variable and a 10% threshold for ASD was used as an indicator of residual imbalance. We then used conditional logistic regression models accounting for these matched patient strata to assess for independent associations between procedural GPI administration and in-hospital outcomes.

Baseline characteristics were reported as means for continuous variables and proportions for categorical variables. Differences between groups were compared using Fisher's exact testing for categorical

variables and Student's *t*-tests for continuous variables. All analyses were performed using R version 3.2.1.[20]

3 | RESULTS

Between January 2010 and September 2015, a total of 177 963 PCIs were performed at 47 hospitals throughout Michigan. Among those, 4303 (2.4%) were performed in patients on dialysis. The baseline characteristics of patients stratified by dialysis use are demonstrated in Table 1. Patients on dialysis had more comorbid conditions and experienced significantly worse outcomes after PCI, including increased rates of blood transfusions (11.9% vs. 2.7%; $P < 0.001$), bleeding (4.4% vs. 2.8%; $P < 0.001$), and death (3.5% vs. 1.5%; $P < 0.001$). Notably, patients on dialysis less frequently experienced major bleeding compared with patients not on dialysis (0.6% vs. 1.2%; $P < 0.001$). The most frequent site of arterial access in dialysis patients was the femoral artery (90.3%).

Of the 4303 patients on dialysis who underwent PCI, 113 received abciximab and 456 received eptifibatide. Of those, a total of 13 (11.5%) patients in the abciximab group and 72 (15.8%) patients in the eptifibatide group met at least one exclusion criteria (Fig. 1), leaving 100 and 384 patients in the abciximab and eptifibatide groups, respectively. Patients who received eptifibatide were more frequently white (66.7% vs. 45.0%; $P < 0.001$); had higher pre-procedural hemoglobin levels (11.3 g/dL vs. 10.7 g/dL; $P < 0.001$); and less frequently had a history of myocardial infarction (36.5% vs. 52.0%; $P = 0.005$) (Table 2). Prior to matching, there were no significant differences among in-hospital outcomes between patients treated with eptifibatide compared with abciximab: need for transfusion (18.8% vs. 18.0%; $P = 0.86$), bleeding (10.2% vs. 10.0%; $P = 0.96$), major bleeding (1.3% vs. 2.0%; $P = 0.60$), repeat PCI (1.3% vs. 1.0%; $P = 0.81$), and death (4.4% vs. 8.0%; $P = 0.15$).

3.1 | Outcomes

After optimal full matching, the ASDs were <10% for most matched variables (Fig. 2), indicating globally similar baseline characteristics within matched strata (Table 2). Of note, the pre-procedural rate of clopidogrel, prasugrel, and ticagrelor administration was 79.2%, 8.9%, and 4.0% for patients receiving eptifibatide and 74.5%, 6.4%, and 3.3% for patients receiving abciximab, respectively (Table 2). There were no significant differences in the adjusted rates and odds of in-hospital outcomes between patients receiving eptifibatide compared with abciximab, respectively: the need for transfusion (14.5% vs. 16.4%; aOR: 1.15; 95%CI: 0.55-2.40; $P = 0.70$), bleeding (8.8% vs. 12.5%; aOR: 1.47; 95%CI: 0.64-3.40; $P = 0.36$), major bleeding (0.3% vs. 1.7%; aOR: 4.68; 95%CI: 0.42-52.3; $P = 0.21$), repeat PCI (1.9% vs. 0.6%; aOR: 0.38; 95%CI: 0.03-4.23; $P = 0.43$), and death (1.3% vs. 2.2%; aOR: 1.53; 95%CI: 0.26-9.05; $P = 0.64$) (Fig. 3).

Of the 384 patients who received eptifibatide, 224 (58.3%) received the medication post-procedurally as well as intra-procedurally whereas the remainder only received it intra-procedurally. In an unadjusted analysis, of the 224 patients who received eptifibatide in the intra- and post-procedural period 13 (5.8%) patients died, whereas only 4 of the 140 patients (2.5%) who received eptifibatide only during the procedure died. Among the patients treated with abciximab, there were four deaths among patients who received the medication intra-procedurally and post-procedurally (n/N = 4/61; 6.6%), and four deaths among those treated with abciximab only during the procedure (n/N = 4/39; 10.3%). The small number of patients in each group limited our ability to further investigate the effect of post-procedural GPI administration on outcomes.

4 | DISCUSSION

Using a large regional registry of patients undergoing PCI, we evaluated the safety of two commonly used GPIs, abciximab and eptifibatide, in dialysis patients undergoing PCI. Our study has three major findings. First, despite being contraindicated in dialysis, eptifibatide was used approximately 3.5 times more often than abciximab. Second, after propensity matching there were no significant differences in important in-hospital outcomes between the two drugs. Third, the frequency of GPI administration among dialysis patients was generally low; however, the rates of bleeding in this select population were high.

The use of GPIs around the time of PCI has been shown to reduce ischemic complications when added to UFH, although often at the expense of increased bleeding complications.[13,21,22] Therefore, clinical practice guidelines recommend carefully considering GPI administration in populations at a high risk of bleeding events, like patients with kidney disease.[18] Nevertheless, in a landmark paper, Tsai et al[9] discovered that nearly a quarter of patients on dialysis undergoing PCI were treated with a contraindicated medication such as eptifibatide.[9] Despite this highly publicized and alarming statistic, we found that eptifibatide continues to be the most frequently prescribed GPI among dialysis patients undergoing PCI.

The reasons why eptifibatide continues to be used when contraindicated in dialysis remains unclear, though we speculate that many factors may play a role. First, eptifibatide is less expensive than abciximab which may drive the increased utilization of eptifibatide.[23] Furthermore, eptifibatide may be more readily available for emergent administration in the catheterization lab. Second, physicians may not be aware of the contraindications to eptifibatide. If this is the case, clinically useful electronic medical records should play an important role in reducing this type of error.

The benefit of GPIs in the management of coronary artery disease was demonstrated through a series of large randomized controlled trials which found a 33% reduction in the risk of death, nonfatal MI, or urgent revascularization at 30 days among patients undergoing PCI.[24] These initial trials primarily compared GPIs to placebo. The TARGET trial was a multicenter evaluation of tirofiban versus abciximab among patients undergoing PCI with the intent to perform stenting.[25] The primary endpoint was a composite of death, nonfatal MI, or urgent target-vessel revascularization at 30 days. The investigators discovered a higher rate of the primary endpoint among patients treated with tirofiban compared with abxicimab (7.6% vs. 6.0%; hazard ratio = 1.26; 95%CI: 1.01-1.57; $P = 0.038$). However, there was a higher rate of Thrombolysis in Myocardial Infarction (TIMI) minor bleeding among

TABLE 1 Baseline characteristics and outcomes of patients by dialysis use

Variable	On dialysis (n = 4303)	Not on dialysis (n = 173 660)	P-value
Demographics			
Age (years)	65.23 ± 11.37	65.06 ± 12.04	0.35
Male gender	2573/4303 (59.8%)	115 853/173 658 (66.7%)	<0.001
Body mass index (kg/m^2)	30.17 ± 8.73	30.62 ± 7.53	<0.001
White race	2708/4303 (62.9%)	150 543/173 660 (86.7%)	<0.001
Black or African-American race	1460/4303 (33.9%)	18 375/173 660 (10.6%)	<0.001
Comorbidities			
Current/recent smoker (within 1 year)	837/4299 (19.5%)	51 038/173 579 (29.4%)	<0.001
Hypertension	4182/4300 (97.3%)	147 813/173 600 (85.1%)	<0.001
Dyslipidemia	3727/4294 (86.8%)	142 400/173 505 (82.1%)	<0.001
Family history of premature CAD	586/4301 (13.6%)	31 486/173 606 (18.1%)	<0.001
Prior MI	2086/4303 (48.5%)	60 363/173 626 (34.8%)	<0.001
Prior heart failure	2301/4301 (53.5%)	27 032/173 587 (15.6%)	<0.001
Prior valve surgery/procedure	131/4298 (3.0%)	3022/173 575 (1.7%)	<0.001
Prior PCI	2311/4303 (53.7%)	78 780/173 629 (45.4%)	<0.001
Prior CABG	1035/4302 (24.1%)	31 911/173 609 (18.4%)	<0.001
Cerebrovascular disease	1347/4298 (31.3%)	26 314/173 592 (15.2%)	<0.001
Peripheral arterial disease	1655/4300 (38.5%)	27 078/173 600 (15.6%)	<0.001
Chronic lung disease	1242/4299 (28.9%)	32 541/173 593 (18.7%)	<0.001
Diabetes mellitus	3143/4303 (73.0%)	64 990/173 619 (37.4%)	<0.001
Heart failure within 2 weeks	1391/4300 (32.3%)	18 587/173 586 (10.7%)	<0.001
Cardiomyopathy or left ventricular systolic dysfunction	948/4302 (22.0%)	17 911/173 618 (10.3%)	<0.001
Cardiogenic shock within 24 h	127/4303 (3.0%)	3069/173 610 (1.8%)	<0.001
Cardiac arrest within 24 h	84/4303 (2.0%)	3370/173 578 (1.9%)	0.96
Pre-PCI left ventricular ejection fraction (%)	47.45 ± 14.52	52.03 ± 12.76	<0.001
Pre-procedure hemoglobin (g/dL)	10.76 ± 1.79	13.50 ± 1.88	<0.001
CAD presentation			
No symptom, no angina	336/4303 (7.8%)	8805/173 615 (5.1%)	<0.001
Symptom unlikely to be ischemic	121/4303 (2.8%)	4037/173 615 (2.3%)	0.037
Stable angina	412/4303 (9.6%)	22 827/173 615 (13.1%)	<0.001
Unstable angina	1687/4303 (39.2%)	73 331/173 615 (42.2%)	<0.001
Non-STEMI	1455/4303 (33.8%)	36 673/173 615 (21.1%)	<0.001
STEMI or equivalent	292/4303 (6.8%)	27 942/173 615 (16.1%)	<0.001
P2Y12 inhibitor administration			
Pre-procedural clopidogrel	1992/4303 (46.3%)	61 108/173 660 (35.2%)	<0.001
Pre-procedural prasugrel	93/4303 (2.2%)	6013/173 660 (3.5%)	<0.001
Pre-procedural ticagrelor[a]	51/2134 (2.4%)	2849/81 870 (3.5%)	0.006
Procedural characteristics			
Intra-aortic balloon pump	124/4301 (2.9%)	4399/173 616 (2.5%)	0.150
Other mechanical ventricular support	91/4298 (2.1%)	1471/173 586 (0.8%)	<0.001
Femoral artery access site	3838/4302 (89.2%)	138 287/173 621 (79.6%)	<0.001
Radial artery access site	438/4302 (10.2%)	34 739/173 621 (20.0%)	<0.001
Cardiogenic shock at start of PCI	133/4301 (3.1%)	3578/173 543 (2.1%)	<0.001
PCI indication			
Immediate PCI for STEMI	250/4302 (5.8%)	25 043/173 617 (14.4%)	<0.001
PCI for STEMI (unstable, >12 h from symptom onset)	28/4302 (0.7%)	1418/173 617 (0.8%)	0.23
PCI for STEMI (stable, >12 h from symptom onset)	21/4302 (0.5%)	451/173 617 (0.3%)	0.004
PCI for STEMI (stable after successful full-dose thrombolysis)	1/4302 (0.0%)	556/173 617 (0.3%)	<0.001

(Continues)

TABLE 1 (Continued)

Variable	On dialysis (n = 4303)	Not on dialysis (n = 173 660)	P-value
Rescue PCI for STEMI (after failed full-dose thrombolytics)	4/4302 (0.1%)	906/173 617 (0.5%)	<0.001
PCI for high-risk non-STEMI or unstable angina	2826/4302 (65.7%)	98 409/173 617 (56.7%)	<0.001
Staged PCI	162/4302 (3.8%)	7525/173 617 (4.3%)	0.070
Other	1010/4302 (23.5%)	39 309/173 617 (22.6%)	0.196
In-hospital outcomes			
Stent thrombosis	5/4303 (0.1%)	328/173 660 (0.2%)	0.28
Repeat PCI	24/4303 (0.6%)	724/173 660 (0.4%)	0.158
Major bleeding	23/3911 (0.6%)	1758/144 904 (1.2%)	<0.001
Blood transfusion	510/4299 (11.9%)	4745/173 563 (2.7%)	<0.001
Bleeding	189/4299 (4.4%)	4852/173 560 (2.8%)	<0.001
Death	151/4303 (3.5%)	2523/173 660 (1.5%)	<0.001

Data are presented as n/N (%) or mean ± standard deviation where appropriate. CABG, coronary artery bypass grafting; CAD, coronary artery disease; IABP, intra-aortic balloon pump; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.
[a]Data on ticagrelor administration was collected beginning on January 1, 2013.

patients treated with abciximab compared with tirofiban (4.3% vs. 2.8%; $P < 0.001$), thus demonstrating the careful balance between ischemic and bleeding complications with these drugs.[25] The current study also demonstrates the balance between these two complications. Patients treated with eptifibatide had lower adjusted rates of bleeding complications but a higher rate of repeat PCI (ie, ischemic complication) compared with abciximab; however, these differences were not statistically significant.

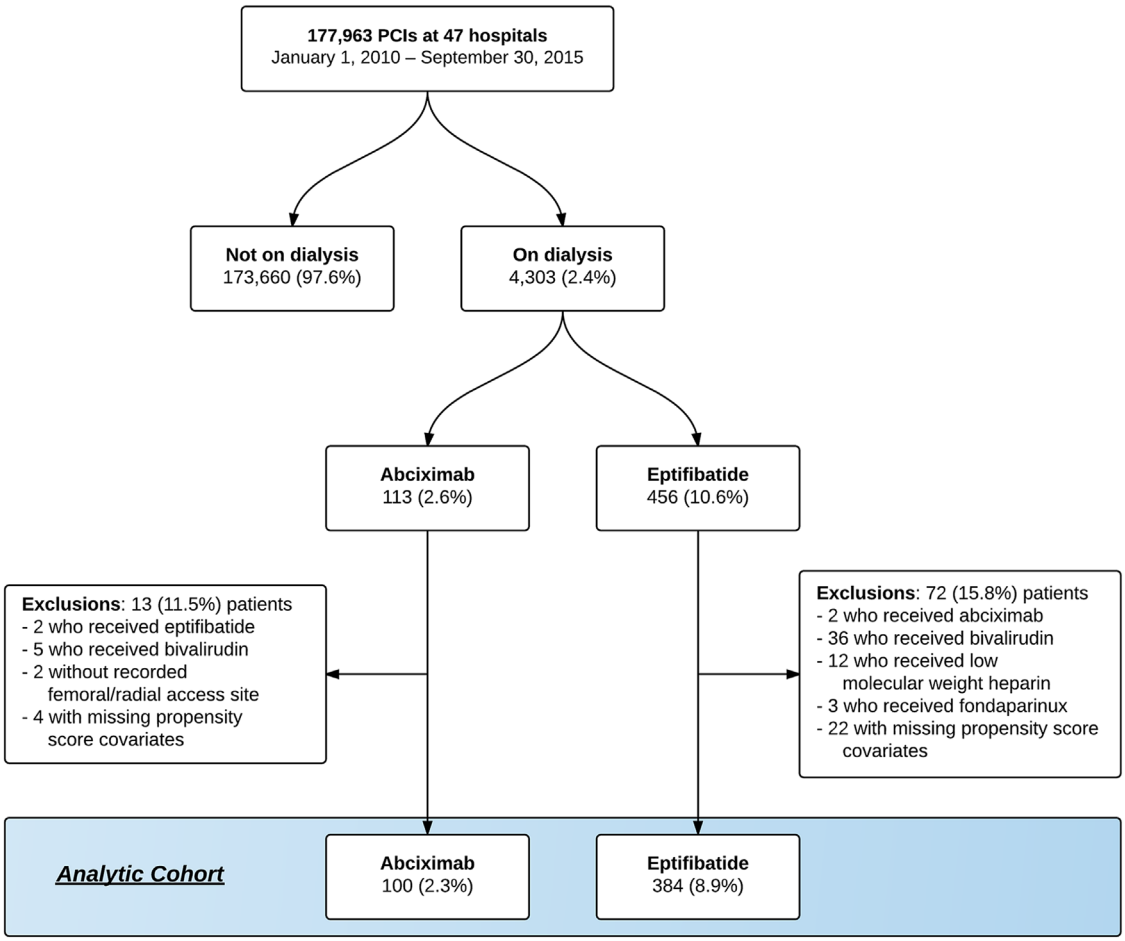

FIGURE 1 Study flow diagram. PCI, percutaneous coronary intervention

TABLE 2 Baseline characteristics of dialysis patients receiving eptifibatide versus abciximab before and after matching

	Before matching				After matching			
	Eptifibatide (n = 384) (%)	Abciximab (n = 100) (%)	Standardized difference (%)	P-value	Eptifibatide (n = 384)	Abciximab (n = 100) (%)	Standardized difference (%)	P-value
Demographics								
Age (years)	64.63 ± 11.73	64.18 ± 11.46	−3.8	0.73	64.22	64.49	2.3	0.85
Male	55.5	53.0	5.0	0.66	49.0	53.0	−8.0	0.57
Body mass index (kg/m^2)	30.5	30.7	1.6	0.89	30.1	30.7	5.5	0.74
White race	66.7	45.0	−45.3	<0.001	48.8	48.8	0.0	>0.99
Black or African-American race	30.5	48.0	37.3	0.001	47.8	45.6	−4.6	0.44
Comorbidities								
Current/recent smoker (within 1 year)	20.3	18.0	−5.8	0.61	19.2	21.5	5.7	0.67
Hypertension	95.1	97.0	9.3	0.41	97.9	96.1	−8.6	0.42
Dyslipidemia	85.4	81.0	−12.2	0.28	82.1	86.7	12.7	0.37
Family history of premature CAD	15.4	10.0	−15.3	0.17	13.2	11.4	−5.0	0.69
Prior MI	36.5	52.0	32.0	0.005	48.8	47.9	−2.0	0.88
Prior heart failure	45.3	52.0	13.4	0.23	48.3	51.1	5.7	0.68
Prior valve surgery/procedure	1.6	4.0	17.1	0.13	2.2	4.2	14.2	0.39
Prior PCI	40.6	50.0	19.0	0.092	44.9	48.6	7.3	0.57
Prior CABG	16.1	25.0	23.1	0.040	22.0	22.0	0.0	>0.99
Cerebrovascular disease	25.0	29.0	9.1	0.42	30.2	27.5	−6.1	0.67
Peripheral arterial disease	28.1	35.0	15.1	0.18	32.5	30.7	−4.1	0.76
Chronic lung disease	25.3	30.0	10.8	0.34	29.0	29.2	0.5	0.97
Diabetes mellitus	68.2	73.0	10.3	0.36	73.3	72.9	−1.0	0.94
Heart failure within 2 weeks	26.0	35.0	20.0	0.076	27.5	31.0	7.8	0.56
Cardiomyopathy or left ventricular systolic dysfunction	17.4	23.0	14.3	0.20	18.3	22.1	9.8	0.45
Cardiogenic shock within 24 h	3.9	7.0	14.8	0.19	1.5	0.9	−2.9	0.48
Cardiac arrest within 24 h	2.3	2.0	−2.3	0.84	0.0	0.0	0.0	>0.99
Pre-PCI left ventricular ejection fraction (%)	48.0 ± 12.9	46.4 ± 13.0	−12.2	0.28	47.8	47.5	−1.9	0.87
Pre-procedure hemoglobin (g/dL) (%)	11.3 ± 2.1	10.7 ± 1.6	−31.4	<0.001	11.0	10.8	−8.1	0.47
CAD presentation								
No symptom, no angina	7.3	4.0	−13.2	0.24	4.5	4.5	0.0	>0.99
Symptom unlikely to be ischemic	1.3	3.0	13.3	0.25	1.2	1.2	0.0	>0.99
Stable angina	9.4	8.0	−4.8	0.67	10.1	10.1	0.0	>0.99

(Continues)

TABLE 2 (Continued)

	Before matching				After matching			
	Eptifibatide (n = 384) (%)	Abciximab (n = 100) (%)	Standardized difference (%)	P-value	Eptifibatide (n = 384)	Abciximab (n = 100) (%)	Standardized difference (%)	P-value
Unstable angina	31.0	28.0	−6.5	0.56	30.5	30.5	0.0	>0.99
Non-STEMI	32.0	42.0	21.1	0.061	40.6	40.6	0.0	>0.99
STEMI or equivalent	19.0	15.0	−10.4	0.36	13.1	13.1	0.0	>0.99
Pre- and intra-procedural antiplatelet therapy								
Clopidogrel	75.8	71.0	−10.8	0.33	79.2	74.5	11.1	0.42
Prasugrel	10.4	9.0	−4.8	0.68	8.9	6.4	9.5	0.50
Ticagrelor[a]	4.2	4.0	−0.8	0.94	4.0	3.3	3.7	0.80
Aspirin	90.6	97.0	26.7	0.037	87.6	97.8	−39.8	0.008
Procedural characteristics								
IABP	4.2	6.0	8.8	0.43	1.8	1.8	0.0	>0.99
Other mechanical ventricular support	1.8	4.0	14.6	0.19	1.2	1.2	0.0	>0.99
Femoral artery access site	88.5	88.0	−1.7	0.88	89.1	86.7	−7.3	0.58
Radial artery access site	11.5	12.0	1.7	0.88	10.9	13.3	7.3	0.58
Cardiogenic shock at start of PCI	4.2	6.0	8.8	0.43	1.2	2.1	4.4	0.32
PCI indication								
Immediate PCI for STEMI	17.4	12.0	−14.7	0.19	12.7	12.1	−1.4	0.67
PCI for STEMI (unstable, >12 h from symptom onset)	1.3	0.0	−12.9	0.25	0.0	0.0	0.0	>0.99
PCI for STEMI (stable, >12 h from symptom onset)	1.0	2.0	8.6	0.44	0.4	0.9	4.7	0.67
PCI for STEMI (stable after successful full-dose thrombolysis)	0.0	0.0	0.0	<0.001	0.0	0.0	0.0	<0.001
Rescue PCI for STEMI (after failed full-dose thrombolytic)	0.0	1.0	22.1	0.050	0.0	0.0	0.0	>0.99
PCI for high-risk non-STEMI or unstable angina	53.9	65.0	22.4	0.047	63.3	66.5	6.4	0.28
Staged PCI	0.8	0.0	−9.9	0.38	0.0	0.0	0.0	>0.99
Other	25.5	20.0	−12.8	0.25	23.6	20.4	−7.4	0.28

Data are presented as percentages (%) or means ± standard deviations where appropriate. CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; STEMI, ST-segment elevation myocardial infarction; IABP, intra-aortic balloon pump.

[a]Data on ticagrelor administration was collected beginning on January 1, 2013.

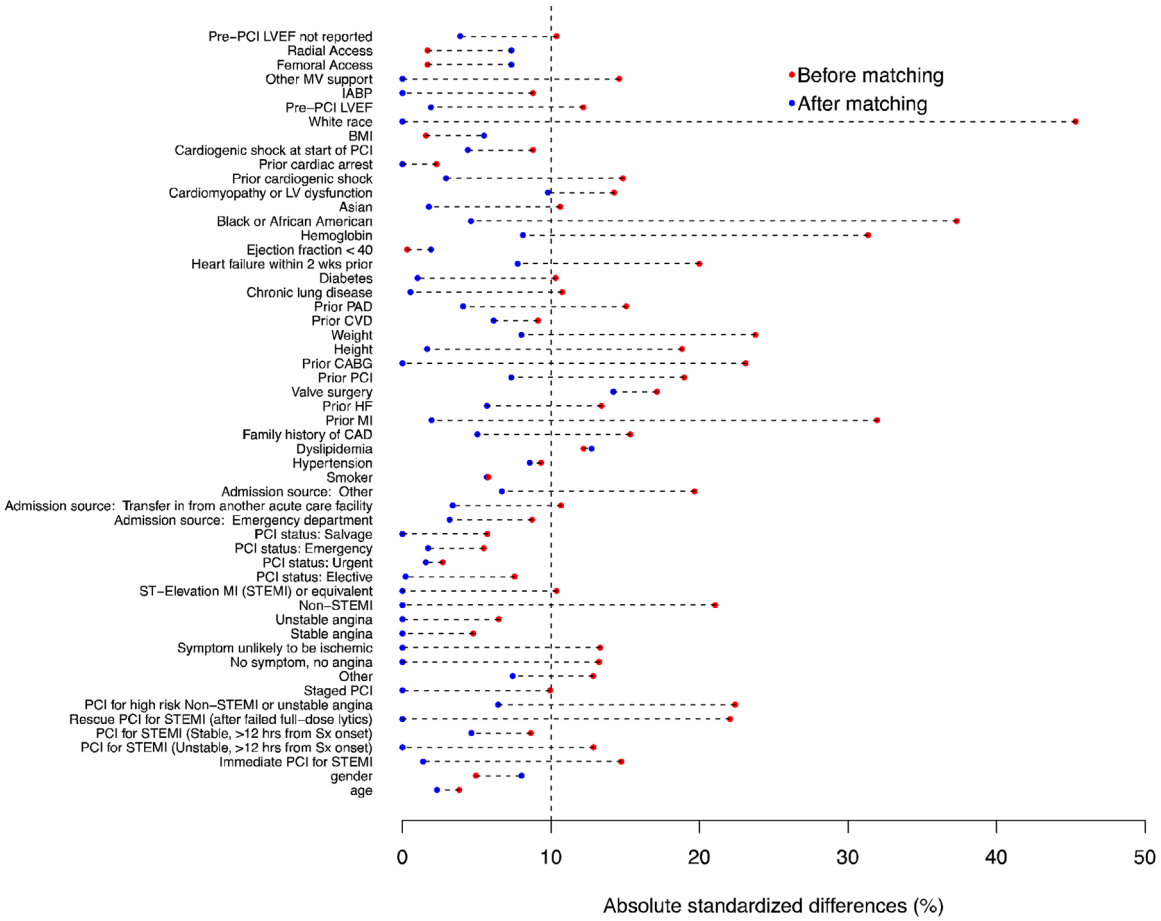

FIGURE 2 Plot of absolute standardized differences before and after matching. Absolute standardized differences before and after matching in dialysis patients receiving eptifibatide compared with abciximab. CABG, coronary artery bypass grafting; CAD, coronary artery disease; CVD, cerebrovascular disease; HF, heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; Sx, symptoms

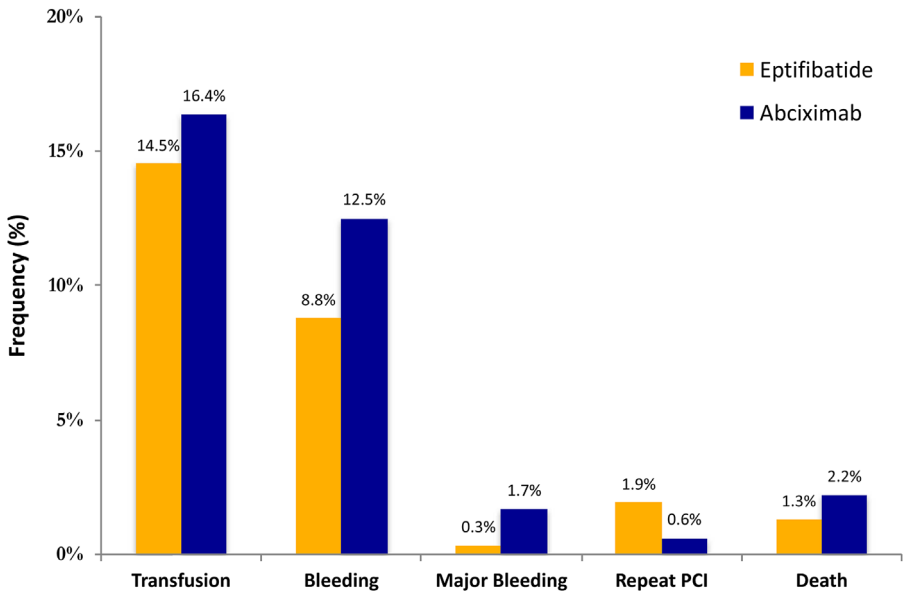

FIGURE 3 Adjusted event rates of in-hospital outcomes in the matched cohort. Bar graph demonstrating in-hospital outcome rates prior to matching among dialysis patients receiving eptifibatide compared with abciximab. All comparisons are non-significant ($P > 0.2$ for all). PCI, percutaneous coronary intervention

Although we were unable to determine the reasons for the continued use of eptifibatide in this high-risk population, it is important to note that we did not find significant differences in the rates of in-hospital bleeding, transfusion, or mortality among dialysis patients who received eptifibatide compared with abciximab.[9,10] A similar finding was noted in a recent study by Barnes et al[10] where they found no significant differences in the rates of peri-procedural bleeding and 30-day mortality among dialysis patients who received eptifibatide during PCI at a Veterans Affairs hospital, although the confidence intervals around the point estimates were wide. Also of note, although Tsai et al[9] demonstrated an increased risk of bleeding among dialysis patients who were treated with a contraindicated medication, eptifibatide use was associated with a significantly increased risk of in-hospital bleeding only in the subgroup of patients presenting with ACS. In an unadjusted analysis, we discovered a higher frequency of in-hospital death among patients who were treated with eptifibatide in the intra-procedural and post-procedural time periods compared with patients who only received intra-procedural eptifibatide. It is possible that continued eptifibatide treatment after the procedure may result in accumulation of the drug in dialysis patients leading to a higher rate of adverse events. Of course, such a finding is confounded by the fact that procedural complications or other patient characteristics may be associated with post-procedural GPI use. Due to the limited number of patients in our study, we did not perform any subgroup analyses out of concern for type I errors resulting from multiple testing.

4.1 | Limitations

There are several important limitations that deserve specific mention. First, as previously noted, we were unable to determine the rationale for GPI administration which may have resulted in inadequate matching. For example, a modest proportion of patients may have received eptifibatide in a provisional fashion due to unmeasured circumstances that occurred during PCI (ie, extreme thrombus burden, ongoing ischemia, etc.). These factors may represent confounding variables associated with the non-random administration of these drugs. Although we attempted to account for the non-random administration of the studied medications through propensity-matching techniques, due to the retrospective nature of this study, we were unable to account for all potential confounders. Second, wide confidence intervals around the point estimates for the adjusted odds ratios for each outcome may be related to our small sample size and limited power to detect a true association. Nevertheless, the direction of the point estimates suggests increased harm with abciximab, not eptifibatide. Third, all hospitals participating in this registry are actively engaged in statewide collaborative quality improvement initiatives. As such, these findings may not be generalizable to hospitals that do not participate in such initiatives.[26] Lastly, we did not collect data on medication dosages or the timing of medication administration relative to the patient's subsequent dialysis session. This may have an important impact on the safety and efficacy of these drugs as prior research has demonstrated that medications are frequently dosed incorrectly in patients with renal insufficiency.[2,11,27] Furthermore, prior research suggests that hemodialysis can effectively reverse the antithrombotic effects of eptifibatide, potentially affecting the decision to use the drug and its impact on clinical outcomes.[14,28,29]

5 | CONCLUSION

Although eptifibatide is contraindicated in patients on dialysis, it was used approximately 3.5 times more often than abciximab during PCI. However, in a propensity-matched analysis, we discovered similar safety outcomes between eptifibatide and abciximab among dialysis patients who underwent PCI. These findings suggest the need for further investigation into the reasons why eptifibatide continues to be used in this population and why there are no significant differences in outcomes.

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DISCLAIMER

Although Blue Cross Blue Shield of Michigan (BCBSM) and BMC2 work collaboratively, the opinions, beliefs, and viewpoints expressed by the author do not necessarily reflect the opinions, beliefs, and viewpoints of BCBSM or any of its employees.

CONFLICT OF INTEREST

Hitinder S. Gurm receives research funding from Blue Cross Blue Shield of Michigan, the National Institutes of Health and is a consultant for Osprey Medical. None of the authors have any conflicts directly relevant to this study.

AUTHORS' CONTRIBUTIONS

Hitinder Gurm and Milan Seth had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Sukul, Seth, Gurm. Acquisition, analysis, or interpretation of data: Schreiber, Hanzel, Khandelwal, Cannon, LaLonde, Gurm. Drafting of the manuscript: Sukul. Critical revision of the manuscript for important intellectual content: Schreiber, Hanzel, Khandelwal, Cannon, LaLonde, Gurm. Statistical analysis: Seth. Obtained funding and study supervision: Gurm.

AUTHORSHIP DECLARATION

All authors listed meet he authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors, and all authors are in agreement with the manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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