The Comparative Safety and Effectiveness of Bivalirudin Versus Heparin Monotherapy in Patients on Dialysis Undergoing Percutaneous Coronary Intervention: Insights from the Blue Cross Blue Shield of Michigan Cardiovascular Consortium (BMC2)

Running Title: *Anticoagulation During PCI in Dialysis Patients*

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ABSTRACT

Background:

Dialysis patients are at a higher risk of bleeding after PCI; however, due to their exclusion from randomized clinical trials, the optimal antithrombotic regimen for this population remains unknown. We sought to evaluate the comparative safety and effectiveness of bivalirudin monotherapy versus unfractionated heparin (UFH) monotherapy in dialysis patients undergoing percutaneous coronary intervention (PCI).

Methods:

We included dialysis patients who underwent PCI in a multicenter registry between January 2010 and September 2015 at 47 Michigan hospitals. We compared in-hospital outcomes between bivalirudin versus UFH; excluding those treated with glycoprotein IIb/IIIa inhibitors. Optimal full matching was used to account for the non-random use of these drugs.

Results:

Of 177,963 patients who underwent PCI, 4,303 (2.4%) were on dialysis. Among those, 1,257 (29.2%) received bivalirudin monotherapy and 2,112 (49.1%) received UFH monotherapy. Patients treated with bivalirudin had fewer comorbidities. After matching, there were no significant differences in outcomes between those who received bivalirudin versus UFH: bleeding (adjusted odds ratio: 0.67; 95% confidence interval: 0.41–1.07; P=0.093); major bleeding (0.81; 0.19–3.50; P=0.77); transfusion (1.01; 0.77–1.33; P=0.96); repeat PCI (0.57; 0.14–2.24; P=0.42); stent thrombosis (0.56; 0.05–5.83; P=0.63); and death (0.84; 0.46–1.51; P=0.55).

Conclusions:

We found no significant differences in in-hospital outcomes between bivalirudin and UFH monotherapy among dialysis patients undergoing PCI. Randomized clinical trials are needed to determine the optimal anticoagulant regimen for this population.

Word count: 227 words (max 250 words)

Keywords: Percutaneous coronary intervention; chronic kidney disease; anticoagulant; dialysis; outcomes.

ABBREVIATIONS

CKD = chronic kidney disease

PCI = percutaneous coronary intervention

UFH = unfractionated heparin

GPI = glycoprotein IIb/IIIa inhibitor

BMC2 = Blue Cross Blue Shield of Michigan Cardiovascular Consortium

NCDR = National Cardiovascular Data Registry

CAD = coronary artery disease

STEMI = ST-segment elevation myocardial infarction

NSTEMI = non-ST-segment elevation myocardial infarction

IABP = intra-aortic balloon pump

aOR = adjusted odds ratio

CI = confidence interval

INTRODUCTION

Patients on dialysis suffer death from cardiovascular causes at rates five to 30 times higher than the general population, making cardiovascular disease the leading cause of death in patients with end-stage renal disease (1). Chronic kidney disease (CKD) is associated with an increased risk of both bleeding and thrombosis due to multiple hemostatic perturbations (2,3). Furthermore, these patients experience increased rates of bleeding and reduced survival after percutaneous coronary intervention (PCI) when compared with patients without CKD (4-8). In fact, progressively worse outcomes after PCI are associated with increasingly severe stages of CKD, with the poorest outcomes occurring in patients on dialysis (5).

Despite this increased risk, patients on dialysis are underrepresented in, or excluded from important cardiovascular randomized controlled trials, resulting in a remarkable dearth of evidence to inform treatment in this high-risk population (9,10). Specifically, patients on dialysis have been underrepresented or excluded from trials evaluating the safety and effectiveness of unfractionated heparin (UFH) compared with bivalirudin (11-18). Many of these clinical trials demonstrated a reduction in bleeding complications without a significant difference in ischemic outcomes in patients treated with bivalirudin compared with UFH with or without glycoprotein IIb/IIIa inhibitors (GPIs) (11-16). Recently, studies have shown similar safety and effectiveness between bivalirudin monotherapy and UFH monotherapy in patients undergoing PCI, reigniting interest in UFH monotherapy as a more cost-effective treatment strategy (19,20).

To our knowledge, there are few studies assessing the use of antithrombotic medications in dialysis patients undergoing PCI (21,22). Given the paucity of evidence, we sought to assess the comparative safety and effectiveness of bivalirudin monotherapy versus UFH monotherapy in dialysis patients undergoing PCI using a multicenter registry in the state of Michigan.

METHODS

Study population

We performed a retrospective analysis on data collected by the Blue Cross Blue Shield of Michigan Cardiovascular Consortium (BMC2), a 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 (23,24). Briefly, this is a prospective, multicenter, statewide registry of patients undergoing PCI at any non-federal hospital in Michigan. For the current study, we evaluated consecutive patients undergoing PCI between January 2010 and September 2015 at 47 hospitals.

Study Groups

We initially divided patients into two groups, those on dialysis and not on dialysis prior to PCI. Patients were considered to be on dialysis if they were undergoing either hemodialysis or peritoneal dialysis on an ongoing basis because of renal failure prior to PCI. To compare the safety and effectiveness of procedural bivalirudin and UFH, we stratified patients on dialysis by administration of these two drugs. The BMC2 PCI registry does not routinely collect the dosages of bivalirudin or UFH administered during PCI.

We excluded patients who received procedural or pre-procedural low molecular weight heparin and/or fondaparinux as well as patients who had no recorded anticoagulant administered in the procedural time period. We also excluded patients who received a concomitant GPI, since GPI use is frequently restricted to higher risk anatomic subsets, or for bailout use secondary to suboptimal procedural results or complications. Of note, patients receiving procedural bivalirudin may have received pre-procedural UFH. Furthermore, a small fraction of patients

receiving procedural bivalirudin also had documented administration of procedural UFH (e.g. UFH is sometimes used during radial access cases). The impact of this subgroup on in-hospital outcomes was assessed in a sensitivity analysis excluding these patients.

Study outcomes

All primary outcomes were measured during the incident hospitalization when PCI was performed. In-hospital outcomes included bleeding, presumed major bleeding, the need for transfusion, repeat PCI, stent thrombosis, and death due to any cause. Stent thrombosis was defined as thrombosis at the site of original stent placement demonstrated on repeat angiography. Repeat PCI was defined as repeat intervention during the incident hospitalization on the lesion that was initially treated. Bleeding, defined as per the National Cardiovascular Data Registry (NCDR), included an event within 72 hours 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 (25). The need for transfusion was defined as the receipt of ≥1 unit of red blood cell or whole blood transfusion after PCI. Presumed major bleeding was defined as a decrease in baseline hemoglobin by >5 g/dL.

Statistical analysis

Propensity scores were estimated using logistic regression models adjusting for baseline patient clinical and demographic variables (supplemental table 1). Optimal full matching was used to create matched patient strata constructed of patients generally similar in terms of baseline characteristics containing varying numbers of patients with (cases) and without (controls) the

covariate of interest (bivalirudin or UFH). As opposed to greedy matching, full matching allows treatment group members to share a control group member as long as it reduces the average distance between matches (26,27). Exact matching was required on coronary artery disease (CAD) presentation (ST-segment elevation myocardial infarction [STEMI], non-ST-segment elevation myocardial infarction [NSTEMI], unstable angina, stable angina, or other), race (white vs. non-white), cardiogenic shock within 24 hours prior to or at the start of PCI, use of an intra-aortic balloon pump (IABP) or other mechanical ventricular support devices, and pre-procedural cardiac arrest. Stratified standardized differences using full match strata were used to assess the adequacy of the match in terms of covariate balance, with a threshold of 10% used to identify cases of substantial residual imbalance. Reported outcome rates were weighted by full match strata, and conditional logistic regression models accounting for matched patient strata were utilized to assess for independent association between procedural use of bivalirudin and UFH, and clinical outcomes. A similar full matching technique was used for the sensitivity analysis. All analyses were performed using R version 3.2.1 (28).

RESULTS

Baseline characteristics

A total of 177,963 PCIs were performed between January 2010 and September 2015, of which 4,303 (2.4%) were on dialysis patients. The baseline characteristics of patients stratified by dialysis use are shown in Table 1. Generally, 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), NCDR 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).

Of the 4,303 patients on dialysis who underwent PCI, 109 (2.5%) received low molecular weight heparin, 13 (0.3%) received fondaparinux, 614 (14.3%) received a GPI, and 215 (5.0%) had no recorded procedural anticoagulant. A total of 934 (2.3%) patients met at least one exclusion criteria, leaving 3,369 patients in the final cohort, of which 1,257 received bivalirudin monotherapy and 2,112 received UFH monotherapy. Patients receiving bivalirudin were more frequently white (73.3% vs. 56.7%; P < 0.001) and had fewer comorbid conditions (Table 2). They were also less likely to experience pre-procedural cardiogenic shock (1.7% vs. 2.9%, P = 0.026), receive IABP support (1.5% vs. 3.1%, P = 0.003) or mechanical ventricular support (0.8% vs. 2.8%, P < 0.001) (Table 2). Prior to matching, patients treated with bivalirudin monotherapy had lower rates of transfusion (8.7% vs. 11.9%; P = 0.003), bleeding (2.7% vs 4.1%; P = 0.038), and in-hospital mortality (2.2% vs 3.4%; P = 0.051) after PCI compared with those treated with UFH monotherapy (Figure 1).

Outcomes

After optimal full matching, the adjusted absolute standardized difference was <10% on all matched variables (Figure 2) with generally similar baseline characteristics within matched strata (Table 2). There were no significant differences in outcomes after adjusting for matched strata between patients treated with bivalirudin compared with UFH: bleeding (adjusted odds ratio [aOR] 0.67; 95% confidence interval [CI] 0.41–1.07; P=0.093); major bleeding (aOR 0.81; 95% CI 0.19–3.50; P=0.77); transfusion (aOR 1.01; 95% CI 0.77–1.33; P=0.96); repeat PCI (aOR 0.57; 95% CI 0.14–2.24; P=0.42); stent thrombosis (aOR 0.56; 95% CI 0.05–5.83; P=0.63); and death (aOR 0.84; 95% CI 0.46–1.51; P=0.55) (Figure 3).

After matching, patients treated with bivalirudin monotherapy more frequently underwent femoral access PCI (89.9%) compared with UFH monotherapy (85.8%; ASD 13.0%; P=0.002; Table 2). Due to this imbalance, we evaluated whether bivalirudin was significantly associated with vascular access site after adjusting for clinical factors. We found that bivalirudin monotherapy was significantly associated with a reduced likelihood of radial access (aOR 0.71; 95% CI: 0.56–0.91; P=0.007). We then conducted a stratified analysis of bivalirudin monotherapy (n=1,144) versus UFH monotherapy (n=1,869) among patients who underwent femoral access PCI. Consistent with the overall findings, we found no significant differences in all studied outcomes including bleeding (aOR 0.63; 95% CI 0.38–1.04; P=0.073), major bleeding (aOR 1.06; 95% CI 0.23–4.86; P=0.94), transfusion (aOR 0.86; 95% CI 0.63–1.17; P=0.32), repeat PCI (aOR 0.75; 95% CI 0.18–3.15; P=0.69), stent thrombosis (aOR 2.45; 95% CI 0.15–39.7; P=0.53), and death (aOR 1.09; 95% CI 0.59–2.00; P=0.79). Of note, we did not evaluate the impact of these drugs among patients who underwent radial access PCI given the small number of events in this subgroup.

In a sensitivity analysis, we excluded 186 (14.8%) patients from the bivalirudin monotherapy group who also received procedural UFH (supplemental table S2). Consistent with the primary results, after matching, there were no significant differences in in-hospital outcomes between the two treatment groups (supplemental figure S1).

DISCUSSION

In this retrospective, multicenter, observational study examining patients on dialysis undergoing PCI, we compared the safety and effectiveness of bivalirudin monotherapy versus UFH monotherapy. To our knowledge, this is the largest multicenter study assessing the use of these two anticoagulation strategies in this high-risk population. The key finding from this study was the lack of significant differences in clinically important in-hospital outcomes between patients on dialysis who received bivalirudin monotherapy compared with UFH monotherapy.

Consistent with prior research, we demonstrated that patients on dialysis experienced inferior outcomes after PCI compared with those not on dialysis, further highlighting the importance of understanding the nuances of peri-procedural treatment in this high-risk population (4,5,7,8,29). Given the lack of randomized controlled trials informing care, well-designed observational studies are needed.

Numerous randomized controlled trials have demonstrated a reduction in bleeding events and non-inferiority for ischemic events associated with bivalirudin when compared to UFH plus GPI therapy (11-15). Furthermore, observational studies and post-hoc analyses of these trials have shown that the benefit of bivalirudin is preserved in CKD patients; however, as previously noted, these studies tended to exclude or underrepresent patients on dialysis (7,8,29,30).

In 2010, Delhaye *et al* published a single-center retrospective analysis evaluating the safety and effectiveness of bivalirudin and UFH monotherapy in 396 dialysis-dependent patients who underwent PCI (21). Similar to our findings, they found no significant difference in clinical endpoints among patients treated with bivalirudin versus UFH. There are many potential reasons for this negative finding. First, unlike prior observational studies and randomized trials, we excluded patients who received a GPI from this analysis, given that GPI use in a provisional

manner may be associated with a high-risk subset of patients. As a recent meta-analysis suggests, the increased rates of bleeding seen with UFH in prior clinical trials comparing UFH and bivalirudin may be attributable to the GPI strategy used in these trials (31). Second, our findings are consistent with the recently published NAPLES III trial which demonstrated no significant difference in rates of major bleeding between bivalirudin and UFH among patients at increased risk of bleeding undergoing PCI (32). However, this trial also excluded patients with end-stage renal disease.

Lastly, we did not collect information regarding the specific dose of administered anticoagulant drugs, nor do we have details regarding the relative timing of each patient's subsequent dialysis session in relation to the timing of anticoagulant administration. Therefore, differences in medication dosages as well as the timing of dialysis could partially account for these findings (33). Nevertheless, after adjusting for known differences between patients receiving bivalirudin compared with UFH, these medications resulted in similar in-hospital safety and effectiveness profiles. This finding has important clinical and economic implications warranting further study, as UFH monotherapy is substantially less expensive than bivalirudin monotherapy (34).

Limitations

The findings from this study should be interpreted with specific caveats. First, all hospitals participating in this registry are actively engaged in statewide collaborative quality improvement initiatives. Therefore, these findings may not be generalizable to hospitals that do not participate in such initiatives (35). Second, our findings represent associations, and should not be interpreted as implying causation. Third, as mentioned above, we did not collect data on

medication dosages, laboratory testing evaluating the effectiveness of anticoagulation (e.g., activated clotting time), or the timing of medication administration relative to the patient's subsequent dialysis session. Furthermore, we were only able to examine short-term outcomes that occurred during the incident hospitalization. Long-term outcomes may differ from these findings and warrants further investigation. Lastly, we do not know the reason behind the selection of specific antithrombotic medications. The rationale for the use of these drugs may be associated with higher or lower risk subgroups, though we attempted to minimize bias using optimal full matching.

Conclusions

We demonstrated similar safety and effectiveness of bivalirudin monotherapy compared with UFH monotherapy among dialysis patients who underwent PCI. Given the substantial cost difference between UFH and bivalirudin monotherapy (34), and in the absence of randomized data to the contrary, our findings suggest that UFH monotherapy may be a safe and potentially cost-effective anticoagulant strategy in this high-risk subgroup of patients undergoing PCI. Further evaluation of this anticoagulant regimen in patients on dialysis is needed.

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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.

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Authors' Contributions: Hitinder Gurm and Milan Seth had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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FIGURE LEGENDS

Figure 1: In-hospital outcome rates before matching.

Bar graph demonstrating in-hospital outcome rates prior to matching among dialysis patients receiving bivalirudin monotherapy compared with unfractionated heparin monotherapy.

Abbreviations: UFH = unfractionated heparin; NCDR = National Cardiovascular Data Registry; PCI = percutaneous coronary intervention.

Figure 2: Plot of absolute standardized differences before and after matching.

Absolute standardized differences before and after matching in dialysis patients receiving bivalirudin compared with unfractionated heparin.

Abbreviations: PCI = percutaneous coronary intervention; LV = left ventricular; PAD = peripheral artery disease; CVD = cerebrovascular disease; CABG = coronary artery bypass grafting; HF = heart failure; MI = myocardial infarction; CAD = coronary artery disease; STEMI = ST-segment elevation myocardial infarction; Sx = symptoms.

Figure 3: Adjusted odds ratios of in-hospital outcomes in the matched cohort.

Adjusted odds ratios with 95% confidence intervals displayed. Adjusted bivalirudin and UFH event rates presented on the right side of the figure.

Abbreviations: UFH = unfractionated heparin; NCDR = National Cardiovascular Data Registry; PCI = percutaneous coronary intervention

Table 1: Baseline characteristics and outcomes of patients by dialysis use.

Variable	On dialysis (*n*=4,303)	Not on dialysis (*n*=173,660)	P value
Demographics			
Age (years)	65.23 ± 11.37	65.06 ± 12.04	0.35
Male gender	2,573/4,303 (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	2,708/4,303 (62.9%)	150,543/173,660 (86.7%)	< 0.001
Black or African American race	1,460/4,303 (33.9%)	18,375/173,660 (10.6%)	< 0.001
Comorbidities			
Current/recent smoker (within 1 year)	837/4,299 (19.5%)	51,038/173,579 (29.4%)	< 0.001
Hypertension	4,182/4,300 (97.3%)	147,813/173,600 (85.1%)	< 0.001
Dyslipidemia	3,727/4,294 (86.8%)	142,400/173,505 (82.1%)	< 0.001
Family history of premature CAD	586/4,301 (13.6%)	31,486/173,606 (18.1%)	< 0.001
Prior MI	2,086/4,303 (48.5%)	60,363/173,626 (34.8%)	< 0.001
Prior heart failure	2,301/4,301 (53.5%)	27,032/173,587 (15.6%)	< 0.001
Prior valve surgery/procedure	131/4,298 (3.0%)	3,022/173,575 (1.7%)	< 0.001
Prior PCI	2,311/4,303 (53.7%)	78,780/173,629 (45.4%)	< 0.001
Prior CABG	1,035/4,302 (24.1%)	31,911/173,609 (18.4%)	< 0.001
Cerebrovascular disease	1,347/4,298 (31.3%)	26,314/173,592 (15.2%)	< 0.001
Peripheral arterial disease	1,655/4,300 (38.5%)	27,078/173,600 (15.6%)	< 0.001
Chronic lung disease	1,242/4,299 (28.9%)	32,541/173,593 (18.7%)	< 0.001

Diabetes mellitus	3,143/4,303 (73.0%)	64,990/173,619 (37.4%)	< 0.001
Heart failure within 2 Weeks	1,391/4,300 (32.3%)	18,587/173,586 (10.7%)	< 0.001
Cardiomyopathy or left ventricular systolic dysfunction	948/4,302 (22.0%)	17,911/173,618 (10.3%)	< 0.001
Cardiogenic shock within 24 Hours	127/4,303 (3.0%)	3,069/173,610 (1.8%)	< 0.001
Cardiac arrest within 24 Hours	84/4,303 (2.0%)	3,370/173,578 (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	336/4,303 (7.8%)	8,805/173,615 (5.1%)	< 0.001
Symptom unlikely to be ischemic	121/4,303 (2.8%)	4,037/173,615 (2.3%)	0.037
Stable angina	412/4,303 (9.6%)	22,827/173,615 (13.1%)	< 0.001
Unstable angina	1,687/4,303 (39.2%)	73,331/173,615 (42.2%)	< 0.001
Non-STEMI	1,455/4,303 (33.8%)	36,673/173,615 (21.1%)	< 0.001
STEMI or equivalent	292/4,303 (6.8%)	27,942/173,615 (16.1%)	< 0.001
P2Y12 Inhibitor Administration			
Pre-procedural clopidogrel	1,992/4,303 (46.3%)	61,108/173,660 (35.2%)	< 0.001
Pre-procedural prasugrel	93/4,303 (2.2%)	6,013/173,660 (3.5%)	< 0.001
Pre-procedural ticagrelor*	51/2,134 (2.4%)	2,849/81,870 (3.5%)	0.006
Procedural Characteristics			
Intra-aortic balloon pump	124/4,301 (2.9%)	4,399/173,616 (2.5%)	0.15

Other mechanical ventricular support	91/4,298 (2.1%)	1,471/173,586 (0.8%)	< 0.001
Femoral artery access site	3,838/4,302 (89.2%)	138,287/173,621 (79.6%)	< 0.001
Radial artery access site	438/4,302 (10.2%)	34,739/173,621 (20.0%)	< 0.001
Cardiogenic Shock at Start of PCI	133/4,301 (3.1%)	3,578/173,543 (2.1%)	< 0.001
PCI Indication			
Immediate PCI for STEMI	250/4,302 (5.8%)	25,043/173,617 (14.4%)	< 0.001
PCI for STEMI (Unstable, >12 hours from symptom onset)	28/4,302 (0.7%)	1,418/173,617 (0.8%)	0.23
PCI for STEMI (Stable, >12 hours from symptom onset)	21/4,302 (0.5%)	451/173,617 (0.3%)	0.004
PCI for STEMI (Stable after successful full-dose thrombolysis)	1/4,302 (0.0%)	556/173,617 (0.3%)	< 0.001
Rescue PCI for STEMI (after failed full-dose thrombolytics)	4/4,302 (0.1%)	906/173,617 (0.5%)	< 0.001
PCI for high risk Non-STEMI or unstable angina	2,826/4,302 (65.7%)	98,409/173,617 (56.7%)	< 0.001
Staged PCI	162/4,302 (3.8%)	7,525/173,617 (4.3%)	0.070
Other	1,010/4,302 (23.5%)	39,309/173,617 (22.6%)	0.196
In-hospital Outcomes			
Stent thrombosis	5/4,303 (0.1%)	328/173,660 (0.2%)	0.28
Repeat PCI	24/4,303 (0.6%)	724/173,660 (0.4%)	0.158
Major bleeding	23/3,911 (0.6%)	1,758/144,904 (1.2%)	< 0.001
Blood transfusion	510/4,299 (11.9%)	4,745/173,563 (2.7%)	< 0.001

NCDR bleeding	189/4,299 (4.4%)	4,852/173,560 (2.8%)	< 0.001
Death	151/4,303 (3.5%)	2,523/173,660 (1.5%)	< 0.001

Data are presented as n/N (%) or mean ± standard deviation where appropriate.

** Data on ticagrelor administration was collected beginning on January 1, 2013.*

Abbreviations: 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; NCDR = National Cardiovascular Data Registry.

Table 2: Baseline characteristics of dialysis patients receiving bivalirudin monotherapy versus unfractionated heparin monotherapy before and after matching.

	Before matching				After matching			
	Heparin (*n*=2,112)	**Bivalirudin (*n*=1,257)**	**Standardized difference (%)**	**P value**	**Heparin (*n*=2,112)**	**Bivalirudin (*n*=1,257)**	**Standardized difference (%)**	**P value**
Demographics								
Age (years)	65.6±10.9	65.2±11.9	-2.8%	0.44	65.2	65.4	2.0%	0.61
Male	61.2%	59.2%	4.0%	0.27	61.0%	60.1%	1.7%	0.66
Body mass index (kg/m^2)	29.9±8.2	30.4±8.9	5.2%	0.15	30.1	30.2	1.0%	0.78
White race	56.7%	73.3%	34.9%	< 0.001	68.7%	68.7%	0.0%	1.00
Black or African American race	39.8%	23.9%	-34.1%	< 0.001	28.4%	28.7%	0.5%	0.69
Comorbidities								
Current/recent smoker (within 1 year)	19.4%	19.1%	-0.7%	0.85	19.3%	18.7%	-1.5%	0.70
Hypertension	98.1%	97.6%	-2.9%	0.42	97.8%	97.5%	-2.1%	0.62
Dyslipidemia	87.9%	86.3%	-4.8%	0.180	87.2%	87.0%	-0.6%	0.87
Family history of premature CAD	12.0%	15.8%	11.2%	0.002	13.8%	14.1%	1.0%	0.79

Prior MI	51.0%	47.8%	-6.4%	0.075	49.3%	49.5%	0.3%	0.93
Prior heart failure	56.8%	52.4%	-8.8%	0.014	53.9%	54.1%	0.4%	0.93
Prior valve surgery/procedure	3.4%	2.6%	-4.6%	0.20	2.9%	3.0%	0.9%	0.82
Prior PCI	57.3%	52.0%	-10.5%	0.003	55.6%	55.3%	-0.7%	0.86
Prior CABG	23.2%	27.6%	10.2%	0.005	25.9%	26.6%	1.7%	0.67
Cerebrovascular disease	32.3%	31.3%	-2.2%	0.54	31.1%	31.5%	1.0%	0.81
Peripheral arterial disease	39.8%	37.4%	-5.1%	0.156	37.9%	38.4%	1.0%	0.80
Chronic lung disease	29.5%	29.7%	0.4%	0.92	29.2%	30.1%	1.8%	0.65
Diabetes mellitus	74.5%	72.4%	-4.7%	0.191	73.4%	73.5%	0.3%	0.95
Heart failure within 2 weeks	34.5%	30.7%	-8.0%	0.026	31.8%	31.3%	-1.0%	0.80
Cardiomyopathy or left ventricular systolic dysfunction	23.1%	20.8%	-5.4%	0.134	21.6%	21.9%	0.6%	0.87
Cardiogenic shock within 24 hours	2.9%	1.7%	-8.0%	0.026	1.0%	0.9%	-0.9%	0.57
Cardiac arrest within 24 hours	1.8%	1.6%	-1.6%	0.65	0.5%	0.5%	0.0%	1.00
Pre-PCI left ventricular ejection fraction (%)	47.5±14.7	48.8±13.9	9.9%	0.006	48.7	48.6	-0.7%	0.86
Pre-procedure hemoglobin (g/dL)	10.5±1.7	10.9±1.8	19.8%	< 0.001	10.7	10.7	0.0%	0.99

CAD Presentation/Management

No symptom, no angina	7.0%	9.6%	9.4%	0.009	8.2%	8.2%	0.0%	1.00
Symptom unlikely to be ischemic	2.5%	3.3%	4.9%	0.175	2.9%	2.9%	0.0%	1.00
Stable angina	8.7%	12.2%	12.0%	0.001	10.7%	10.7%	0.0%	1.00
Unstable angina	42.1%	37.5%	-9.4%	0.009	40.6%	40.6%	0.0%	1.00
Non-STEMI	35.3%	32.3%	-6.4%	0.074	33.7%	33.7%	0.0%	1.00
STEMI or equivalent	4.4%	5.1%	3.3%	0.35	4.0%	4.0%	0.0%	1.00
P2Y12 Inhibitor Administration								
Pre-procedural clopidogrel	49.8%	44.7%	-10.3%	0.004	48.5%	46.2%	-4.5%	0.26
Pre-procedural prasugrel	2.0%	1.8%	-1.5%	0.69	1.7%	2.1%	2.8%	0.49
Pre-procedural ticagrelor*	1.6%	0.8%	-7.3%	0.043	1.3%	0.6%	-6.2%	0.093
Procedural Characteristics								
IABP	3.1%	1.5%	-10.8%	0.003	0.9%	1.1%	1.7%	0.23
Other mechanical ventricular support	2.8%	0.8%	-13.8%	< 0.001	0.9%	0.6%	-1.9%	0.23
Femoral artery access site	87.7%	90.3%	8.1%	0.025	85.8%	89.9%	13.0%	0.002
Radial artery access site	11.7%	9.2%	-8.1%	0.025	13.5%	9.6%	-12.8%	0.002
Cardiogenic shock at start of PCI	3.3%	1.6%	-10.4%	0.004	1.1%	1.2%	0.7%	0.54

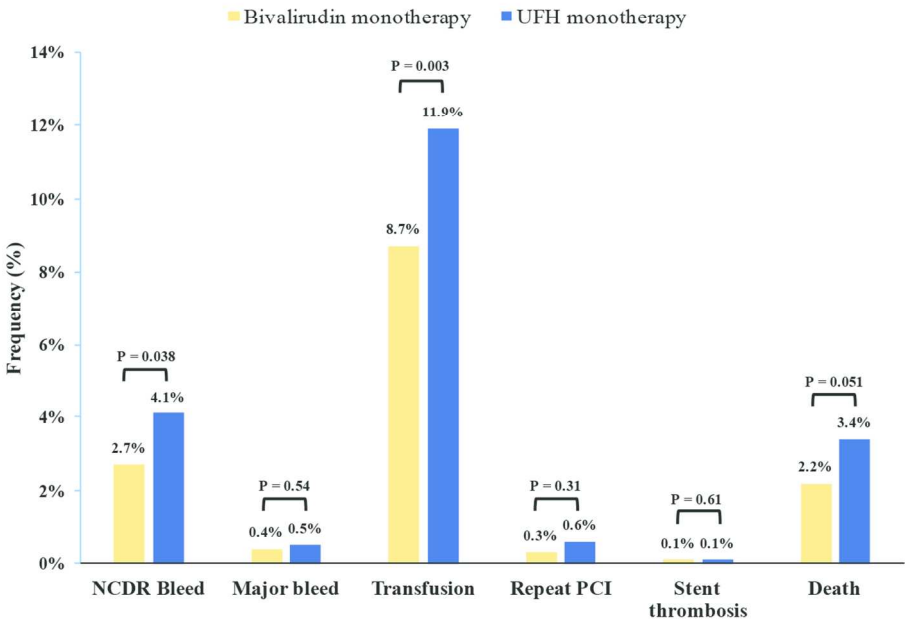
PCI Indication								
Immediate PCI for STEMI	3.5%	4.5%	5.5%	0.128	3.5%	3.5%	-0.1%	0.96
PCI for STEMI (Unstable, >12 hours from symptom onset)	0.7%	0.5%	-2.5%	0.49	0.5%	0.5%	0.1%	0.96
PCI for STEMI (Stable, >12 hours from symptom onset)	0.4%	0.1%	-6.4%	0.073	0.0%	0.0%	0.0%	1.00
PCI for STEMI (Stable after successful full-dose thrombolysis)	0.0%	0.1%	4.7%	0.195	0.0%	0.0%	0.0%	1.00
Rescue PCI for STEMI (after failed full-dose thrombolytic)	0.1%	0.0%	-3.9%	0.28	0.0%	0.0%	0.0%	1.00
PCI for high risk Non-STEMI or unstable angina	69.5%	64.5%	-10.7%	0.003	67.7%	67.3%	-0.8%	0.73
Staged PCI	4.2%	4.4%	1.1%	0.76	4.2%	4.3%	0.2%	0.97
Other	21.7%	25.9%	10.1%	0.005	24.1%	24.5%	0.8%	0.76

Data are presented as percentages (%) or means ± standard deviations where appropriate.

** Data on ticagrelor administration was collected beginning on January 1, 2013.*

Abbreviations: 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.

Figure 1: In-hospital outcome rates before matching.



Bar graph demonstrating in-hospital outcome rates prior to matching among dialysis patients receiving bivalirudin monotherapy compared with unfractionated heparin monotherapy.
Abbreviations: UFH = unfractionated heparin; NCDR = National Cardiovascular Data Registry; PCI = percutaneous coronary intervention.

Figure 1: In-hospital outcome rates before matching.
Bar graph demonstrating in-hospital outcome rates prior to matching among dialysis patients receiving bivalirudin monotherapy compared with unfractionated heparin monotherapy.
Abbreviations: UFH = unfractionated heparin; NCDR = National Cardiovascular Data Registry; PCI = percutaneous coronary intervention.

120x106mm (300 x 300 DPI)

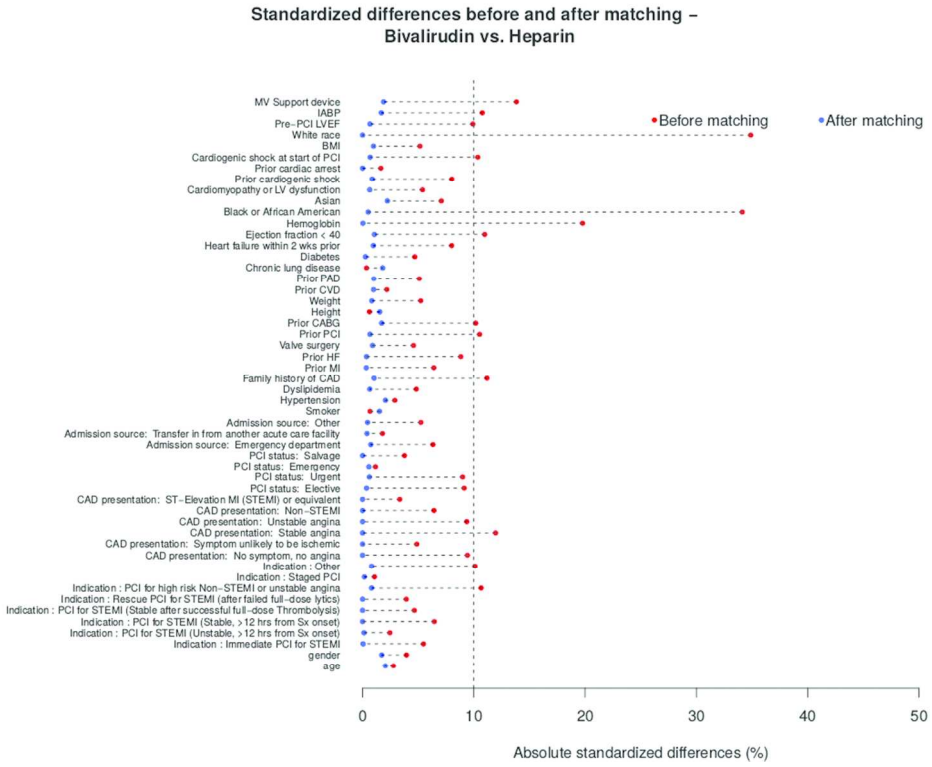
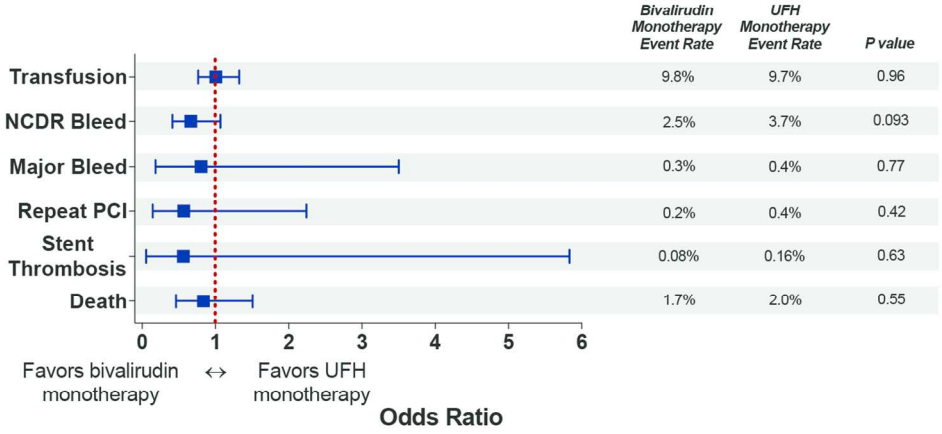


Figure 2: Plot of absolute standardized differences before and after matching.
Absolute standardized differences before and after matching in dialysis patients receiving bivalirudin compared with unfractionated heparin.
Abbreviations: PCI = percutaneous coronary intervention; LV = left ventricular; PAD = peripheral artery disease; CVD = cerebrovascular disease; CABG = coronary artery bypass grafting; HF = heart failure; MI = myocardial infarction; CAD = coronary artery disease; STEMI = ST-segment elevation myocardial infarction; Sx = symptoms.

279x215mm (300 x 300 DPI)

Figure 3: Adjusted odds ratios and event rates of in-hospital outcomes in the matched cohort.



Adjusted odds ratios with 95% confidence intervals displayed. Adjusted bivalirudin and UFH event rates are presented on the right side of the figure.
Abbreviations: UFH = unfractionated heparin; NCDR = National Cardiovascular Data Registry; PCI = percutaneous coronary intervention.

Figure 3: Adjusted odds ratios of in-hospital outcomes in the matched cohort.
Adjusted odds ratios with 95% confidence intervals displayed. Adjusted bivalirudin and UFH event rates presented on the right side of the figure.
Abbreviations: UFH = unfractionated heparin; NCDR = National Cardiovascular Data Registry; PCI = percutaneous coronary intervention

122x82mm (300 x 300 DPI)

Supplementary Material

Table S1: List of covariates included in the propensity score models.

Table S2: Baseline characteristics of dialysis patients receiving bivalirudin monotherapy versus unfractionated heparin monotherapy before and after matching in the sensitivity analysis cohort.

Figure S1: Adjusted odds ratios and event rates of in-hospital outcomes in the matched sensitivity analysis cohort

Table S1: List of covariates included in the propensity score models.

- Age
- Gender
- Race (White*, Black, Asian, other)
- CAD presentation (STEMI, NSTEMI, unstable angina, stable angina, non-ischemic, no symptoms)*
- PCI status (elective, urgent, emergency, salvage)
- PCI indication (primary PCI, PCI for STEMI > 12 hours post-symptom onset, PCI for STEMI after successful or failed thrombolytic therapy, PCI for high risk NSTEMI or unstable angina, staged PCI, other)
- Current or recent smoker (within 1 year)
- Hypertension
- Dyslipidemia
- Family history of premature CAD
- Prior myocardial infarction
- Prior heart failure
- Prior valve surgery/procedure
- Prior PCI
- Prior coronary artery bypass grafting
- Admission source (emergency department, transfer, other)
- Height
- Weight
- Cerebrovascular disease
- Peripheral arterial disease
- Chronic lung disease
- Diabetes mellitus
- Heart failure within 2 weeks
- Cardiomyopathy or left ventricular systolic dysfunction
- Cardiogenic shock within 24 hours*
- Cardiogenic shock at start of PCI*
- Cardiac arrest within 24 hours*
- Pre-procedure hemoglobin
- Use of intra-aortic balloon pump or other mechanical ventricular support device*

* Exact matching required for CAD presentation, white race, cardiogenic shock within 24 hours or at the start of PCI, cardiac arrest, and use of intra-aortic balloon pump or other mechanical ventricular support device

Abbreviations: CAD, coronary artery disease; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention.

Table S2: Baseline characteristics of dialysis patients receiving bivalirudin monotherapy versus unfractionated heparin monotherapy before and after matching in the sensitivity analysis cohort.

	Before matching				After matching			
	Heparin (*n*=2,112)	**Bivalirudin (*n*=1,071)**	**Standardized difference (%)**	**P value**	**Heparin (*n*=2,112)**	**Bivalirudin (*n*=1,071)**	**Standardized difference (%)**	**P Value**
Demographics								
Age (years)	65.6±10.9	65.1±12.0	-4.2%	0.271	65.5	65.5	-0.2%	0.954
Male	61.2%	58.9%	4.6%	0.223	60.2%	59.2%	1.9%	0.640
Body mass index (kg/m^2)	29.9±8.2	30.4±9.1	5.4%	0.156	30.3	30.3	-0.3%	0.930
White race	56.7%	74.1%	36.4%	< 0.001	69.6%	69.6%	0.0%	1.000
Black or African American race	39.8%	22.9%	-36.3%	< 0.001	27.2%	27.9%	1.7%	0.210
Comorbidities								
Current/recent smoker (within 1 year)	19.4%	19.0%	-1.1%	0.779	18.7%	18.5%	-0.5%	0.916
Hypertension	98.1%	97.7%	-2.5%	0.511	98.0%	97.7%	-1.7%	0.686
Dyslipidemia	87.9%	85.9%	-6.1%	0.110	87.0%	86.3%	-2.0%	0.639
Family history of premature CAD	12.0%	15.3%	9.9%	0.009	14.4%	13.6%	-2.3%	0.591
Prior MI	51.0%	48.6%	-4.8%	0.206	49.5%	50.2%	1.5%	0.727
Prior heart failure	56.8%	52.3%	-9.0%	0.017	54.2%	54.1%	-0.1%	0.980

Table S2: Baseline characteristics of dialysis patients receiving bivalirudin monotherapy versus unfractionated heparin monotherapy before and after matching in the sensitivity analysis cohort (continued).

Prior valve surgery/procedure	3.4%	2.7%	-4.1%	0.279	2.9%	3.1%	0.9%	0.819
Prior PCI	57.3%	53.1%	-8.4%	0.027	55.9%	55.3%	-1.1%	0.782
Prior CABG	23.2%	27.8%	10.8%	0.004	28.1%	27.2%	-2.0%	0.636
Cerebrovascular disease	32.3%	31.4%	-2.0%	0.596	31.1%	31.4%	0.5%	0.898
Peripheral arterial disease	39.8%	37.9%	-3.9%	0.304	39.1%	38.0%	-2.4%	0.569
Chronic lung disease	29.5%	30.0%	1.2%	0.759	29.9%	30.2%	0.7%	0.875
Diabetes mellitus	74.5%	73.5%	-2.3%	0.540	75.1%	74.2%	-2.2%	0.611
Heart failure within 2 weeks	34.5%	31.2%	-7.0%	0.064	31.5%	31.7%	0.3%	0.933
Cardiomyopathy or left ventricular systolic dysfunction	23.1%	20.4%	-6.4%	0.091	21.2%	21.1%	-0.3%	0.945
Cardiogenic shock within 24 hours	2.9%	1.6%	-8.5%	0.025	1.0%	0.7%	-1.7%	0.291
Cardiac arrest within 24 hours	1.8%	1.8%	-0.2%	0.959	0.6%	0.6%	0.0%	1.000
Pre-PCI left ventricular ejection fraction (%)	47.5±14.7	49.0±13.8	11.0%	0.004	48.7	48.9	1.8%	0.639
Pre-procedure hemoglobin (g/dL)	10.5±1.7	10.9±1.8	18.6%	< 0.001	10.8	10.8	0.2%	0.958

CAD Presentation

Table S2: Baseline characteristics of dialysis patients receiving bivalirudin monotherapy versus unfractionated heparin monotherapy before and after matching in the sensitivity analysis cohort (continued).

No symptom, no angina	7.0%	9.7%	10.0%	0.008	8.7%	8.7%	0.0%	1.000
Symptom unlikely to be ischemic	2.5%	3.5%	6.1%	0.109	3.1%	3.1%	0.0%	1.000
Stable angina	8.7%	12.0%	11.3%	0.003	10.8%	10.8%	0.0%	1.000
Unstable angina	42.1%	36.3%	-11.8%	0.002	39.0%	39.0%	0.0%	1.000
Non-STEMI	35.3%	33.3%	-4.3%	0.260	34.5%	34.5%	0.0%	1.000
STEMI or equivalent	4.4%	5.1%	3.5%	0.349	3.9%	3.9%	0.0%	1.000
Procedural Characteristics								
IABP	3.1%	1.1%	-12.9%	0.001	0.5%	0.8%	1.7%	0.289
Other mechanical ventricular support	2.8%	0.8%	-14.0%	0.000	0.5%	0.2%	-2.2%	0.216
Femoral artery access site	87.7%	95.1%	25.1%	0.000	86.8%	95.4%	29.0%	0.000
Radial artery access site	11.7%	4.3%	-25.7%	0.000	12.7%	4.3%	-29.3%	0.000
Cardiogenic shock at start of PCI	3.3%	1.6%	-10.2%	0.007	0.8%	1.0%	1.2%	0.342
PCI Indication								
Immediate PCI for STEMI	3.5%	4.7%	6.2%	0.104	3.4%	3.5%	0.4%	0.685

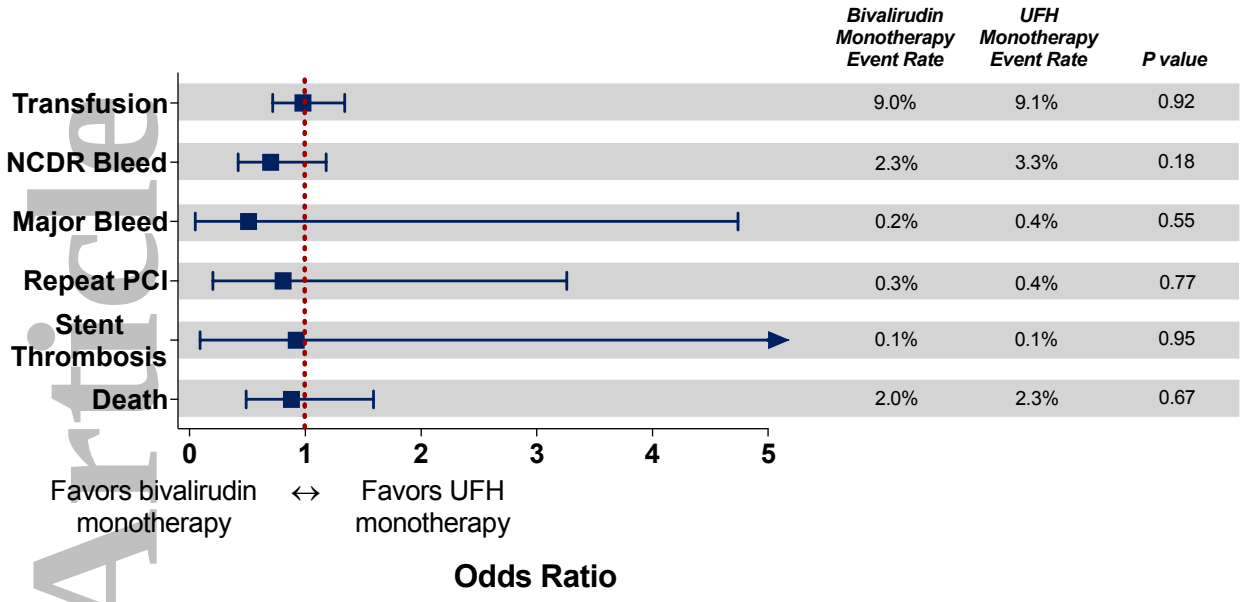
Table S2: Baseline characteristics of dialysis patients receiving bivalirudin monotherapy versus unfractionated heparin monotherapy before and after matching in the sensitivity analysis cohort (continued).

PCI for STEMI (Unstable, >12 hours from symptom onset)	0.7%	0.4%	-3.9%	0.303	0.5%	0.4%	-0.6%	0.822
PCI for STEMI (Stable, >12 hours from symptom onset)	0.4%	0.1%	-6.0%	0.113	0.0%	0.0%	-0.7%	0.617
PCI for STEMI (Stable after successful full-dose thrombolysis)	0.0%	0.1%	5.3%	0.160	0.0%	0.0%	0.0%	1.000
Rescue PCI for STEMI (after failed full-dose thrombolytic)	0.1%	0.0%	-3.8%	0.314	0.0%	0.0%	0.0%	1.000
PCI for high risk Non-STEMI or unstable angina	69.5%	64.5%	-10.6%	0.005	66.7%	66.9%	0.3%	0.898
Staged PCI	4.2%	4.5%	1.6%	0.674	4.5%	4.5%	0.3%	0.948
Other	21.7%	25.7%	9.7%	0.011	24.8%	24.6%	-0.5%	0.867

Data are presented as percentages (%) or means ± standard deviation where appropriate.

Abbreviations: 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.

Figure S1: Adjusted odds ratios and event rates of in-hospital outcomes in the matched sensitivity analysis cohort



Adjusted odds ratios with 95% confidence intervals displayed. Adjusted bivalirudin and UFH event rates are presented on the right side of the figure.
Abbreviations: UFH = unfractionated heparin; NCDR = National Cardiovascular Data Registry; PCI = percutaneous coronary intervention

January 6, 2017

Dr. Hitinder S. Gurm, MD
University of Michigan Health System
Department of Internal Medicine
A. Alfred Taubman Health Care Center
1500 East Medical Center Drive, Room TC B1 226
Ann Arbor, Michigan 48109-0311

RE: CIRCCVINT/2016/004835
The Comparative Safety and Efficacy of Bivalirudin Versus Heparin Monotherapy in Patients on Dialysis Undergoing Percutaneous Coronary Intervention: Insights from the Blue Cross Blue Shield of Michigan Cardiovascular Consortium (BMC2)

Dear Dr. Gurm,

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Thank you very much for submitting your paper to Circulation: Cardiovascular Interventions. We hope you that you will submit a revised version to JAHA: Journal of the American Heart Association.

Sincerely yours,

Barry London, MD, PhD
Editor-in-Chief
JAHA: Journal of the American Heart Association

David P. Faxon, MD
Editor
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Reviewer #1:

Sukul D. et al. report a study evaluating the comparative safety and efficacy of bivalirudin monotherapy as compared to unfractionated heparin (UFH) monotherapy in dialysis patients undergoing percutaneous coronary intervention (PCI). The Authors included dialysis patients who underwent PCI in a multicenter registry between January 2010 and September 2015 at 47 Michigan hospitals. They compared in-hospital outcomes between bivalirudin versus UFH; excluding those treated with glycoprotein IIb/IIIa inhibitors. Optimal full matching was used to account for the non-random use of these drugs. Of 177,963 patients who underwent PCI, 4,303 (2.4%) were on dialysis. Among those, 1,257 (29.2%) received bivalirudin monotherapy and 2,112 (49.1%) received UFH monotherapy. Patients treated with bivalirudin had fewer comorbidities. After matching, there were no significant differences in outcomes between those who received bivalirudin versus UFH: bleeding (adjusted odds ratio: 0.67; 95% confidence interval: 0.41-1.07; P=0.093); major bleeding (0.81; 0.19-3.50; P=0.77); transfusion (1.01; 0.77-1.33; P=0.96); repeat PCI (0.57; 0.14-2.24; P=0.42); stent thrombosis (0.56; 0.05-5.83; P=0.63); and death (0.84; 0.46-1.51; P=0.55). The Authors conclude that no significant differences exist in in-hospital outcomes between bivalirudin and UFH monotherapy in dialysis patients undergoing PCI.

I have the following comments that may improve the clinical relevance of this study:

1) In the Study Limitations, the Authors state that "we did not collect data on medication dosages or the timing of medication administration relative to the patient's subsequent dialysis session". Bivalirudin administration is usually contraindicated in patients with end-stage CKD and /or on dialysis. Dose adjustment is also recommended in patients with GFR>30 mL7min/1.732. The Authors should at least report in the METHODS section the policy of bivalirudin dose in patients in this subset of patients.

We thank the Reviewer for highlighting this important issue. Although dosages adjustments for bivalirudin are recommended among patients with renal impairment, it is not contraindicated in dialysis.(1) The drug's prescriber information states that the bolus dose does not need to be reduced for any degree of renal impairment. Furthermore, the infusion dose should be reduced to 1.75 mg/kg/h for patients with a GFR of 30-59 mL/min; 1 mg/kg/h for patients with a GFR of <30 mL/min; and 0.25 mg/kg/h for patients on hemodialysis (1,2).

The Blue Cross Blue Shield of Michigan Cardiovascular Collaborative (BMC2) PCI registry does not routinely collect drug dosing information; therefore, we were unable to account for variations in the dosages administered of either bivalirudin or unfractionated heparin (UFH). We also do not have information regarding each institution's policy regarding UFH and bivalirudin dosing in patients on dialysis. However, since all hospitals in this study are actively engaged in statewide quality improvement initiatives through BMC2, there is an ongoing focus on ensuring optimal use of drugs and devices.

As requested, we have added a sentence reporting the lack of medication dosage information (page 6, line 17).

"The BMC2 PCI registry does not routinely collect the dosages of bivalirudin or UFH administered during PCI."

2) The same concept is for unfractionated heparin (UFH) administration. The Authors should at least report in the METHODS section the policy of UFH dose in patients in this subset of patients.

As noted above, we were unable to account for institution-specific dosing policies for UFH or bivalirudin. Notably, unfractionated heparin is primarily metabolized by the liver and endothelium, thus no dosage adjustment is required in patients on dialysis (2).

3) In the study limitation, the Authors should acknowledge the lack of data on ACT value in the 2 groups of patients.

We appreciate the Reviewer bringing this point to our attention. We have revised the following sentence to highlight the lack of this data (page 13, line 23).

"Third, as mentioned above, we did not collect data on medication dosages, laboratory testing evaluating the efficacy of anticoagulation (e.g., activated clotting time), or the timing of medication administration relative to the patient's subsequent dialysis session."

4) After matching, radial approach was higher in the dialysis group. This may represent a clinically relevant bias.

We are unsure of the intended meaning behind the Reviewer's comment as we did not match patients by dialysis status. Instead, among patients on dialysis undergoing PCI we matched patients who received bivalirudin monotherapy to those who received heparin monotherapy. The Reviewer may have meant to state, "After matching, radial approach was higher in the **UFH** group." If this is the case, we answer this question more completely in response to comment #2 by Reviewer #2 (see below).

5) Please add the study by Shahzad et al. (Lancet. 2014 Nov 22;384(9957):1849-5 and Briguori et al. (JACC Cardiovasc Interv. 2015 Mar;8(3):414-23) in the discussion.

The study by Shahzad *et. al.* was already included as reference #19. I have added the findings from the NAPLES III trial published by Briguori *et al.* (page 13, line 3):

"Second, our findings are consistent with the recently published NAPLES III trial which demonstrated no significant difference in rates of major bleeding between bivalirudin and UFH among patients at increased risk of bleeding undergoing PCI (32). However, this trial also excluded patients with end-stage renal disease."

Reviewer #2:

In general, this is a well-done retrospective study attempting to report on differences in PCI outcomes in dialysis patients treated with heparin monotherapy or bivalirudin.

1) A key missing component from the dataset is the dose of bivalirudin used. In the setting of dialysis dependency, the dose of bivalirudin is recommended to be decreased from the standard 1.75 mg/kg/h to 0.25 mg/kg/h. Was this done? I would imagine that there would be no way of knowing the patient-level data in this type of system-wide analysis. If dose adjustment was not performed, the impact on bleeding would likely be significant.

Although patient-level data was used in this analysis, as previously noted, the BMC2 PCI registry does not routinely collect data regarding the dose of anticoagulant administered. The impact of drug dose and timing of dialysis relative to drug administration may have an important impact on post-procedural outcomes and should be an area of future investigation. We have identified this limitation (page 13, line 23). Nonetheless, our study provides insight into the effectiveness of these two anticoagulant strategies in real-world practice. We have also taken the liberty of changing the word efficacy to effectiveness in the title.

"Third, as mentioned above, we did not collect data on medication dosages, laboratory testing evaluating the effectiveness of anticoagulation (e.g., activated clotting time), or the timing of medication administration relative to the patient's subsequent dialysis session."

2) Femoral, as opposed to radial access PCI is subject to a greater frequency of bleeding. It appears from Table 2 that even after propensity score matching was performed, the bivalirudin patients had a significantly greater frequency of femoral PCI procedures. This likely would lead to more bleeding in bivalirudin-treated patients.

We agree with the Reviewer and have performed further analysis to evaluate the effect of bivalirudin and UFH monotherapy among patients undergoing femoral access PCI.

To evaluate the effect of chosen vascular access on the impact of bivalirudin vs. heparin on clinical outcomes we first assessed whether bivalirudin was significantly associated with vascular access choice after adjusting for clinical factors including: CAD presentation, PCI status, PCI indication, smoking, hypertension, dyslipidemia, family history of CAD, prior mi, prior heart failure, valve surgery, prior PCI, prior CABG, height, weight, prior cerebrovascular disease, prior peripheral artery disease, chronic lung disease, diabetes, heart failure within 2 weeks, ejection fraction <40%, hemoglobin, race (white, black, Asian, other), admission source, left ventricular dysfunction, cardiogenic shock, and cardiac arrest.

We found that bivalirudin monotherapy was significantly associated with a reduced likelihood of radial access (adjusted OR = 0.71; 95% CI: 0.56–0.91; P= 0.007) after adjusting for baseline covariates.

Given this significant association we pursued a stratified analysis evaluating the effect of bivalirudin vs. heparin on outcomes among patients who underwent femoral access PCI. Among patients undergoing femoral access PCI, there were no significant differences in the studied outcomes (see below).

Outcome	Adjusted Odds Ratio	95% Confidence Interval	P value
Bleeding	0.63	0.38 – 1.04	0.073
Major bleeding	1.06	0.23 – 4.86	0.94
Transfusion	0.86	0.63 – 1.17	0.32
Repeat PCI	0.75	0.18 – 3.15	0.69
Stent thrombosis	2.45	0.15 – 39.7	0.53
Death	1.09	0.59 – 2.00	0.79

Odds ratios greater than 1 are in favor of UFH monotherapy, whereas odds ratios less than 1 are in favor of bivalirudin monotherapy.

We have included these findings in the results section (page 10, line 9) as follows:

"After matching, patients treated with bivalirudin monotherapy more frequently underwent femoral access PCI (89.9%) as compared with UFH monotherapy (85.8%; ASD 13.0%; P=0.002; Table 2). Due to this imbalance, we evaluated whether bivalirudin was significantly associated with vascular access site after adjusting for clinical factors. We found that bivalirudin monotherapy was significantly associated with a reduced likelihood of radial access (aOR 0.71; 95% CI: 0.56–0.91; P=0.007). We then conducted a stratified analysis of bivalirudin monotherapy (n=1,144) versus UFH monotherapy (n=1,869) among patients who underwent femoral access PCI. Consistent with the overall findings, we found no significant differences in all studied outcomes including bleeding (aOR 0.63; 95% CI 0.38–1.04; P=0.073), major bleeding (aOR 1.06; 95% CI 0.23–4.86; P=0.94), transfusion (aOR 0.86; 95% CI 0.63–1.17; P=0.32), repeat PCI (aOR 0.75; 95% CI 0.18–3.15; P=0.69), stent thrombosis (aOR 2.45; 95% CI 0.15–39.7; P=0.53), and death (aOR 1.09; 95% CI 0.59–2.00; P=0.79). Of note, we did not evaluate the impact of these drugs among patients who underwent radial access PCI given the small number of events in this subgroup."

3) Examination of Figure 3 and other data in the manuscript suggest that virtually all odds ratios are in favor of bivalirudin treatment with a lack of significant p values because of the relatively small sample size. This would, of course, be at odds with the stated conclusions.

We appreciate the Reviewer's comments and have revised our stated conclusions (page 14, line 12).

"Given the substantial cost difference between UFH and bivalirudin monotherapy (34), and in the absence of randomized data to the contrary, our findings suggest that UFH monotherapy may be a safe and potentially cost-effective anticoagulant strategy in this high-risk subgroup of

patients undergoing PCI. Further evaluation of this anticoagulant regimen in patients on dialysis is needed."

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The Comparative Safety and Effectiveness of Bivalirudin Versus Heparin Monotherapy in Patients on Dialysis Undergoing Percutaneous Coronary Intervention: Insights from the Blue Cross Blue Shield of Michigan Cardiovascular Consortium (BMC2)

Running Title: *Anticoagulation During PCI in Dialysis Patients*

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ABSTRACT

Background:

Dialysis patients are at a higher risk of bleeding after PCI; however, due to their exclusion from randomized clinical trials, the optimal antithrombotic regimen for this population remains unknown. We sought to evaluate the comparative safety and effectiveness of bivalirudin monotherapy versus unfractionated heparin (UFH) monotherapy in dialysis patients undergoing percutaneous coronary intervention (PCI).

Methods:

We included dialysis patients who underwent PCI in a multicenter registry between January 2010 and September 2015 at 47 Michigan hospitals. We compared in-hospital outcomes between bivalirudin versus UFH; excluding those treated with glycoprotein IIb/IIIa inhibitors. Optimal full matching was used to account for the non-random use of these drugs.

Results:

Of 177,963 patients who underwent PCI, 4,303 (2.4%) were on dialysis. Among those, 1,257 (29.2%) received bivalirudin monotherapy and 2,112 (49.1%) received UFH monotherapy. Patients treated with bivalirudin had fewer comorbidities. After matching, there were no significant differences in outcomes between those who received bivalirudin versus UFH: bleeding (adjusted odds ratio: 0.67; 95% confidence interval: 0.41–1.07; P=0.093); major bleeding (0.81; 0.19–3.50; P=0.77); transfusion (1.01; 0.77–1.33; P=0.96); repeat PCI (0.57; 0.14–2.24; P=0.42); stent thrombosis (0.56; 0.05–5.83; P=0.63); and death (0.84; 0.46–1.51; P=0.55).

Conclusions:

We found no significant differences in in-hospital outcomes between bivalirudin and UFH monotherapy among dialysis patients undergoing PCI. Randomized clinical trials are needed to determine the optimal anticoagulant regimen for this population.

Word count: 227 words (max 250 words)

Keywords: Percutaneous coronary intervention; chronic kidney disease; anticoagulant; dialysis; outcomes.

ABBREVIATIONS

CKD = chronic kidney disease

PCI = percutaneous coronary intervention

UFH = unfractionated heparin

GPI = glycoprotein IIb/IIIa inhibitor

BMC2 = Blue Cross Blue Shield of Michigan Cardiovascular Consortium

NCDR = National Cardiovascular Data Registry

CAD = coronary artery disease

STEMI = ST-segment elevation myocardial infarction

NSTEMI = non-ST-segment elevation myocardial infarction

IABP = intra-aortic balloon pump

aOR = adjusted odds ratio

CI = confidence interval

INTRODUCTION

Patients on dialysis suffer death from cardiovascular causes at rates five to 30 times higher than the general population, making cardiovascular disease the leading cause of death in patients with end-stage renal disease (1). Chronic kidney disease (CKD) is associated with an increased risk of both bleeding and thrombosis due to multiple hemostatic perturbations (2,3). Furthermore, these patients experience increased rates of bleeding and reduced survival after percutaneous coronary intervention (PCI) when compared with patients without CKD (4-8). In fact, progressively worse outcomes after PCI are associated with increasingly severe stages of CKD, with the poorest outcomes occurring in patients on dialysis (5).

Despite this increased risk, patients on dialysis are underrepresented in, or excluded from important cardiovascular randomized controlled trials, resulting in a remarkable dearth of evidence to inform treatment in this high-risk population (9,10). Specifically, patients on dialysis have been underrepresented or excluded from trials evaluating the safety and effectiveness of unfractionated heparin (UFH) compared with bivalirudin (11-18). Many of these clinical trials demonstrated a reduction in bleeding complications without a significant difference in ischemic outcomes in patients treated with bivalirudin compared with UFH with or without glycoprotein IIb/IIIa inhibitors (GPIs) (11-16). Recently, studies have shown similar safety and effectiveness between bivalirudin monotherapy and UFH monotherapy in patients undergoing PCI, reigniting interest in UFH monotherapy as a more cost-effective treatment strategy (19,20).

To our knowledge, there are few studies assessing the use of antithrombotic medications in dialysis patients undergoing PCI (21,22). Given the paucity of evidence, we sought to assess the comparative safety and effectiveness of bivalirudin monotherapy versus UFH monotherapy in dialysis patients undergoing PCI using a multicenter registry in the state of Michigan.

METHODS

Study population

We performed a retrospective analysis on data collected by the Blue Cross Blue Shield of Michigan Cardiovascular Consortium (BMC2), a 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 (23,24). Briefly, this is a prospective, multicenter, statewide registry of patients undergoing PCI at any non-federal hospital in Michigan. For the current study, we evaluated consecutive patients undergoing PCI between January 2010 and September 2015 at 47 hospitals.

Study Groups

We initially divided patients into two groups, those on dialysis and not on dialysis prior to PCI. Patients were considered to be on dialysis if they were undergoing either hemodialysis or peritoneal dialysis on an ongoing basis because of renal failure prior to PCI. To compare the safety and effectiveness of procedural bivalirudin and UFH, we stratified patients on dialysis by administration of these two drugs. The BMC2 PCI registry does not routinely collect the dosages of bivalirudin or UFH administered during PCI.

We excluded patients who received procedural or pre-procedural low molecular weight heparin and/or fondaparinux as well as patients who had no recorded anticoagulant administered in the procedural time period. We also excluded patients who received a concomitant GPI, since GPI use is frequently restricted to higher risk anatomic subsets, or for bailout use secondary to suboptimal procedural results or complications. Of note, patients receiving procedural bivalirudin may have received pre-procedural UFH. Furthermore, a small fraction of patients

receiving procedural bivalirudin also had documented administration of procedural UFH (e.g. UFH is sometimes used during radial access cases). The impact of this subgroup on in-hospital outcomes was assessed in a sensitivity analysis excluding these patients.

Study outcomes

All primary outcomes were measured during the incident hospitalization when PCI was performed. In-hospital outcomes included bleeding, presumed major bleeding, the need for transfusion, repeat PCI, stent thrombosis, and death due to any cause. Stent thrombosis was defined as thrombosis at the site of original stent placement demonstrated on repeat angiography. Repeat PCI was defined as repeat intervention during the incident hospitalization on the lesion that was initially treated. Bleeding, defined as per the National Cardiovascular Data Registry (NCDR), included an event within 72 hours 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 (25). The need for transfusion was defined as the receipt of ≥1 unit of red blood cell or whole blood transfusion after PCI. Presumed major bleeding was defined as a decrease in baseline hemoglobin by >5 g/dL.

Statistical analysis

Propensity scores were estimated using logistic regression models adjusting for baseline patient clinical and demographic variables (supplemental table 1). Optimal full matching was used to create matched patient strata constructed of patients generally similar in terms of baseline characteristics containing varying numbers of patients with (cases) and without (controls) the

covariate of interest (bivalirudin or UFH). As opposed to greedy matching, full matching allows treatment group members to share a control group member as long as it reduces the average distance between matches (26,27). Exact matching was required on coronary artery disease (CAD) presentation (ST-segment elevation myocardial infarction [STEMI], non-ST-segment elevation myocardial infarction [NSTEMI], unstable angina, stable angina, or other), race (white vs. non-white), cardiogenic shock within 24 hours prior to or at the start of PCI, use of an intra-aortic balloon pump (IABP) or other mechanical ventricular support devices, and pre-procedural cardiac arrest. Stratified standardized differences using full match strata were used to assess the adequacy of the match in terms of covariate balance, with a threshold of 10% used to identify cases of substantial residual imbalance. Reported outcome rates were weighted by full match strata, and conditional logistic regression models accounting for matched patient strata were utilized to assess for independent association between procedural use of bivalirudin and UFH, and clinical outcomes. A similar full matching technique was used for the sensitivity analysis. All analyses were performed using R version 3.2.1 (28).

RESULTS

Baseline characteristics

A total of 177,963 PCIs were performed between January 2010 and September 2015, of which 4,303 (2.4%) were on dialysis patients. The baseline characteristics of patients stratified by dialysis use are shown in Table 1. Generally, 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), NCDR 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).

Of the 4,303 patients on dialysis who underwent PCI, 109 (2.5%) received low molecular weight heparin, 13 (0.3%) received fondaparinux, 614 (14.3%) received a GPI, and 215 (5.0%) had no recorded procedural anticoagulant. A total of 934 (2.3%) patients met at least one exclusion criteria, leaving 3,369 patients in the final cohort, of which 1,257 received bivalirudin monotherapy and 2,112 received UFH monotherapy. Patients receiving bivalirudin were more frequently white (73.3% vs. 56.7%; P < 0.001) and had fewer comorbid conditions (Table 2). They were also less likely to experience pre-procedural cardiogenic shock (1.7% vs. 2.9%, P = 0.026), receive IABP support (1.5% vs. 3.1%, P = 0.003) or mechanical ventricular support (0.8% vs. 2.8%, P < 0.001) (Table 2). Prior to matching, patients treated with bivalirudin monotherapy had lower rates of transfusion (8.7% vs. 11.9%; P = 0.003), bleeding (2.7% vs 4.1%; P = 0.038), and in-hospital mortality (2.2% vs 3.4%; P = 0.051) after PCI compared with those treated with UFH monotherapy (Figure 1).

Outcomes

After optimal full matching, the adjusted absolute standardized difference was <10% on all matched variables (Figure 2) with generally similar baseline characteristics within matched strata (Table 2). There were no significant differences in outcomes after adjusting for matched strata between patients treated with bivalirudin compared with UFH: bleeding (adjusted odds ratio [aOR] 0.67; 95% confidence interval [CI] 0.41–1.07; P=0.093); major bleeding (aOR 0.81; 95% CI 0.19–3.50; P=0.77); transfusion (aOR 1.01; 95% CI 0.77–1.33; P=0.96); repeat PCI (aOR 0.57; 95% CI 0.14–2.24; P=0.42); stent thrombosis (aOR 0.56; 95% CI 0.05–5.83; P=0.63); and death (aOR 0.84; 95% CI 0.46–1.51; P=0.55) (Figure 3).

After matching, patients treated with bivalirudin monotherapy more frequently underwent femoral access PCI (89.9%) compared with UFH monotherapy (85.8%; ASD 13.0%; P=0.002; Table 2). Due to this imbalance, we evaluated whether bivalirudin was significantly associated with vascular access site after adjusting for clinical factors. We found that bivalirudin monotherapy was significantly associated with a reduced likelihood of radial access (aOR 0.71; 95% CI: 0.56–0.91; P=0.007). We then conducted a stratified analysis of bivalirudin monotherapy (n=1,144) versus UFH monotherapy (n=1,869) among patients who underwent femoral access PCI. Consistent with the overall findings, we found no significant differences in all studied outcomes including bleeding (aOR 0.63; 95% CI 0.38–1.04; P=0.073), major bleeding (aOR 1.06; 95% CI 0.23–4.86; P=0.94), transfusion (aOR 0.86; 95% CI 0.63–1.17; P=0.32), repeat PCI (aOR 0.75; 95% CI 0.18–3.15; P=0.69), stent thrombosis (aOR 2.45; 95% CI 0.15–39.7; P=0.53), and death (aOR 1.09; 95% CI 0.59–2.00; P=0.79). Of note, we did not evaluate the impact of these drugs among patients who underwent radial access PCI given the small number of events in this subgroup.

In a sensitivity analysis, we excluded 186 (14.8%) patients from the bivalirudin monotherapy group who also received procedural UFH (supplemental table S2). Consistent with the primary results, after matching, there were no significant differences in in-hospital outcomes between the two treatment groups (supplemental figure S1).

DISCUSSION

In this retrospective, multicenter, observational study examining patients on dialysis undergoing PCI, we compared the safety and effectiveness of bivalirudin monotherapy versus UFH monotherapy. To our knowledge, this is the largest multicenter study assessing the use of these two anticoagulation strategies in this high-risk population. The key finding from this study was the lack of significant differences in clinically important in-hospital outcomes between patients on dialysis who received bivalirudin monotherapy compared with UFH monotherapy.

Consistent with prior research, we demonstrated that patients on dialysis experienced inferior outcomes after PCI compared with those not on dialysis, further highlighting the importance of understanding the nuances of peri-procedural treatment in this high-risk population (4,5,7,8,29). Given the lack of randomized controlled trials informing care, well-designed observational studies are needed.

Numerous randomized controlled trials have demonstrated a reduction in bleeding events and non-inferiority for ischemic events associated with bivalirudin when compared to UFH plus GPI therapy (11-15). Furthermore, observational studies and post-hoc analyses of these trials have shown that the benefit of bivalirudin is preserved in CKD patients; however, as previously noted, these studies tended to exclude or underrepresent patients on dialysis (7,8,29,30).

In 2010, Delhaye *et al* published a single-center retrospective analysis evaluating the safety and effectiveness of bivalirudin and UFH monotherapy in 396 dialysis-dependent patients who underwent PCI (21). Similar to our findings, they found no significant difference in clinical endpoints among patients treated with bivalirudin versus UFH. There are many potential reasons for this negative finding. First, unlike prior observational studies and randomized trials, we excluded patients who received a GPI from this analysis, given that GPI use in a provisional

manner may be associated with a high-risk subset of patients. As a recent meta-analysis suggests, the increased rates of bleeding seen with UFH in prior clinical trials comparing UFH and bivalirudin may be attributable to the GPI strategy used in these trials (31). Second, our findings are consistent with the recently published NAPLES III trial which demonstrated no significant difference in rates of major bleeding between bivalirudin and UFH among patients at increased risk of bleeding undergoing PCI (32). However, this trial also excluded patients with end-stage renal disease.

Lastly, we did not collect information regarding the specific dose of administered anticoagulant drugs, nor do we have details regarding the relative timing of each patient's subsequent dialysis session in relation to the timing of anticoagulant administration. Therefore, differences in medication dosages as well as the timing of dialysis could partially account for these findings (33). Nevertheless, after adjusting for known differences between patients receiving bivalirudin compared with UFH, these medications resulted in similar in-hospital safety and effectiveness profiles. This finding has important clinical and economic implications warranting further study, as UFH monotherapy is substantially less expensive than bivalirudin monotherapy (34).

Limitations

The findings from this study should be interpreted with specific caveats. First, all hospitals participating in this registry are actively engaged in statewide collaborative quality improvement initiatives. Therefore, these findings may not be generalizable to hospitals that do not participate in such initiatives (35). Second, our findings represent associations, and should not be interpreted as implying causation. Third, as mentioned above, we did not collect data on

medication dosages, laboratory testing evaluating the effectiveness of anticoagulation (e.g., activated clotting time), or the timing of medication administration relative to the patient's subsequent dialysis session. Furthermore, we were only able to examine short-term outcomes that occurred during the incident hospitalization. Long-term outcomes may differ from these findings and warrants further investigation. Lastly, we do not know the reason behind the selection of specific antithrombotic medications. The rationale for the use of these drugs may be associated with higher or lower risk subgroups, though we attempted to minimize bias using optimal full matching.

Conclusions

We demonstrated similar safety and effectiveness of bivalirudin monotherapy compared with UFH monotherapy among dialysis patients who underwent PCI. Given the substantial cost difference between UFH and bivalirudin monotherapy (34), and in the absence of randomized data to the contrary, our findings suggest that UFH monotherapy may be a safe and potentially cost-effective anticoagulant strategy in this high-risk subgroup of patients undergoing PCI. Further evaluation of this anticoagulant regimen in patients on dialysis is needed.

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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.

Disclosures:

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 of 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

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FIGURE LEGENDS

Figure 1: In-hospital outcome rates before matching.

Bar graph demonstrating in-hospital outcome rates prior to matching among dialysis patients receiving bivalirudin monotherapy compared with unfractionated heparin monotherapy.

Abbreviations: UFH = unfractionated heparin; NCDR = National Cardiovascular Data Registry; PCI = percutaneous coronary intervention.

Figure 2: Plot of absolute standardized differences before and after matching.

Absolute standardized differences before and after matching in dialysis patients receiving bivalirudin compared with unfractionated heparin.

Abbreviations: PCI = percutaneous coronary intervention; LV = left ventricular; PAD = peripheral artery disease; CVD = cerebrovascular disease; CABG = coronary artery bypass grafting; HF = heart failure; MI = myocardial infarction; CAD = coronary artery disease; STEMI = ST-segment elevation myocardial infarction; Sx = symptoms.

Figure 3: Adjusted odds ratios of in-hospital outcomes in the matched cohort.

Adjusted odds ratios with 95% confidence intervals displayed. Adjusted bivalirudin and UFH event rates presented on the right side of the figure.

Abbreviations: UFH = unfractionated heparin; NCDR = National Cardiovascular Data Registry; PCI = percutaneous coronary intervention