Catheterization and Cardiovascular Interventions 90:724–732 (2017)

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

Devraj Sukul,[1] MD, Milan Seth,[1] MS, Theodore Schreiber,[2] MD, Akshay Khandelwal,[3] MD, Louis A. Cannon,[4] MD, Thomas A. LaLonde,[5] MD, and Hitinder S. Gurm,[1,6*] MD

Background: Dialysis patients are at a higher risk of bleeding after percutaneous coronary intervention (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 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 nonrandom 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.

Key words: percutaneous coronary intervention; chronic kidney disease; anticoagulant; dialysis; outcomes

Additional Supporting Information may be found in the online version of this article.

[1]Department of Internal Medicine, Division of Cardiovascular Medicine, University of Michigan, Ann Arbor, Michigan
[2]Detroit Medical Center-Cardiovascular Institute, Detroit, Michigan
[3]Division of Cardiology, Henry Ford Health System, Detroit, Michigan
[4]McLaren-Northern Michigan Regional Hospital, Petoskey, Michigan
[5]Department of Cardiovascular Medicine, St. John Hospital and Medical Center, Detroit, Michigan
[6]Cardiovascular Medicine, VA Ann Arbor Healthcare System, Ann Arbor, Michigan

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.

Contract grant sponsor: National Institutes of Health T32 postdoctoral research training; Contract grant number: T32-HL-007853.
Contract grant sponsor: Blue Cross Blue Shield of Michigan and Blue Care Network as part of the Blue Cross Blue Shield of Michigan Value Partnerships program. The funding source supported data collection at each site and funded the data-coordinating center but had no role in study concept, interpretation of findings, or in the preparation, final approval or decision to submit the manuscript.

*Correspondence to: Hitinder S. Gurm, MD, 2A 394, 1500 East Medical Ctr Drive,, University of Michigan Cardiovascular Center, Ann Arbor, MI 48109-5853. E-mail: hgurm@med.umich.edu

Received 27 January 2017; Revision accepted 4 February 2017

DOI: 10.1002/ccd.27001
Published online 17 March 2017 in Wiley Online Library (wileyonlinelibrary.com)

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 preprocedural 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 preprocedural 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 hr of PCI that was associated with any of the following: a drop in hemoglobin $\geq$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 $\geq$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 (Supporting Information Table S1). 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 hr prior to or at the start of PCI, use of an intra-aortic balloon pump (IABP) or other mechanical ventricular support devices, and preprocedural 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 performed in patients on dialysis. The baseline characteristics of patients stratified by dialysis use are shown in Table I. 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 II). They were also less likely to experience preprocedural cardiogenic shock (1.7% vs. 3.0%, $P = 0.026$), receive IABP support (1.5% vs. 3.1%, $P = 0.003$) or mechanical ventricular support (0.8% vs. 2.8%, $P < 0.001$) (Table II). 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 (Fig. 1).

Outcomes

After optimal full matching, the adjusted absolute standardized difference (ASD) was <10% on all matched variables (Fig. 2) with generally similar baseline characteristics within matched strata (Table II). 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; $P = 0.55$) (Fig. 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 II). 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.

TABLE I. 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 hr	127/4,303 (3.0%)	3,069/173,610 (1.8%)	< 0.001
Cardiac arrest within 24 hr	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
Preprocedure 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			
Preprocedural clopidogrel	1,992/4,303 (46.3%)	61,108/173,660 (35.2%)	< 0.001
Preprocedural prasugrel	93/4,303 (2.2%)	6,013/173,660 (3.5%)	< 0.001
Preprocedural ticagrelor[a]	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 hr from symptom onset)	28/4,302 (0.7%)	1,418/173,617 (0.8%)	0.23
PCI for STEMI (Stable, >12 hr 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.

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

Abbreviations: CABG, coronary artery bypass grafting; CAD, coronary artery disease; IABP, intra-aortic balloon pump; MI, myocardial infarction; NCDR, National Cardiovascular Data Registry; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

TABLE II. 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 hr	3.0%	1.7%	−8.0%	0.026	1.0%	0.9%	−0.9%	0.57
Cardiac arrest within 24 hr	1.8%	1.6%	−1.7%	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
Preprocedure 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								
Preprocedural clopidogrel	49.8%	44.7%	−10.3%	0.004	48.5%	46.2%	−4.5%	0.26
Preprocedural prasugrel	2.0%	1.8%	−1.5%	0.69	1.7%	2.1%	2.8%	0.49
Preprocedural ticagrelor[a]	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 hr from symptom onset)	0.7%	0.5%	−2.5%	0.49	0.5%	0.5%	0.1%	0.96
PCI for STEMI (Stable, >12 hr 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.

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

Abbreviations: 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.

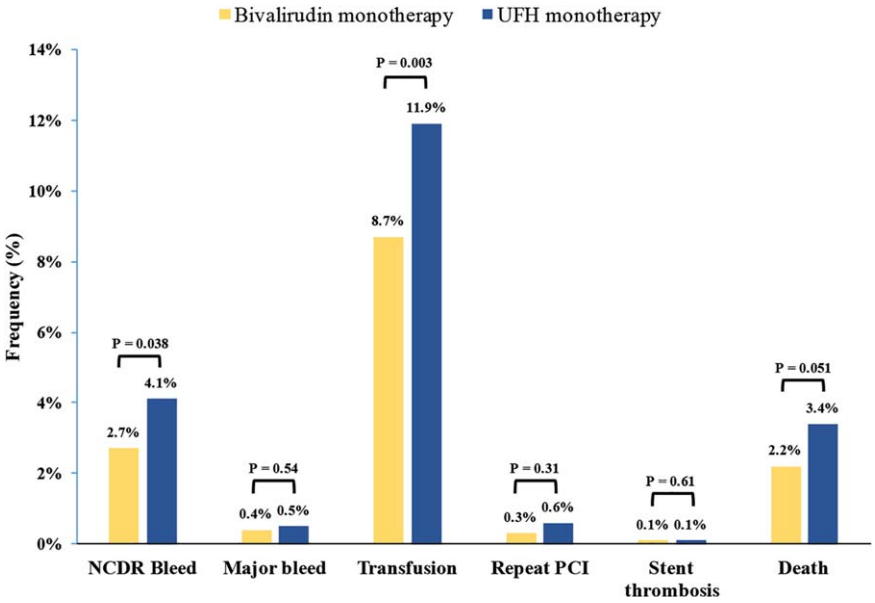

Fig. 1. Bar graph demonstrating in-hospital outcome rates prior to matching among dialysis patients receiving bivalirudin monotherapy compared with unfractionated heparin monotherapy. Abbreviations: NCDR, National Cardiovascular Data Registry; PCI, percutaneous coronary intervention; UFH, unfractionated heparin. [Color figure can be viewed at wileyonlinelibrary.com]

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

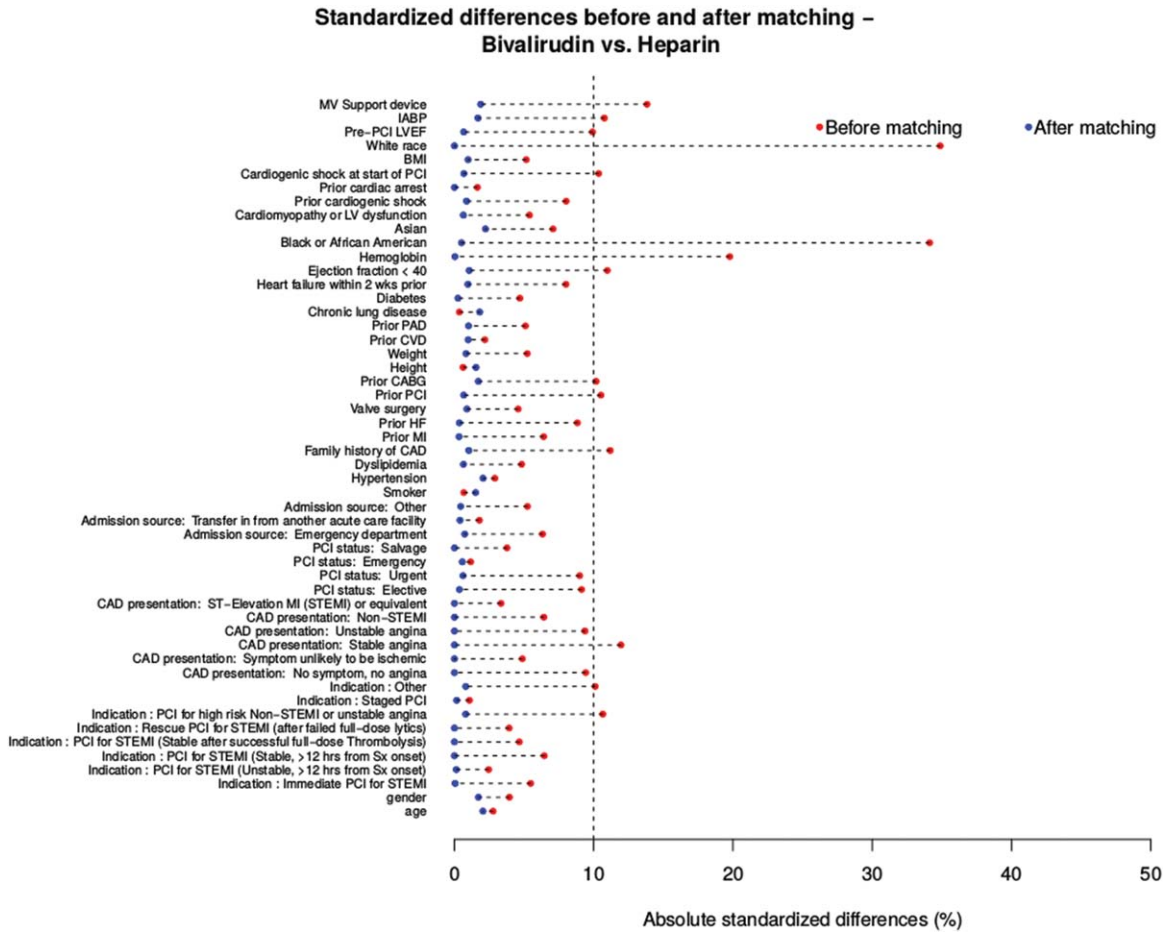

Fig. 2. Absolute standardized differences before and after matching in dialysis patients receiving bivalirudin compared with unfractionated heparin. Abbreviations: BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CVD, cerebrovascular disease; HF, heart failure; IABP, intra-aortic balloon pump; LV, left ventricular; MI, myocardial infarction; MV, mechanical ventricular; PCI, percutaneous coronary intervention; PAD, peripheral artery disease; STEMI, ST-segment elevation myocardial infarction; Sx, symptoms. [Color figure can be viewed at wileyonlinelibrary.com]

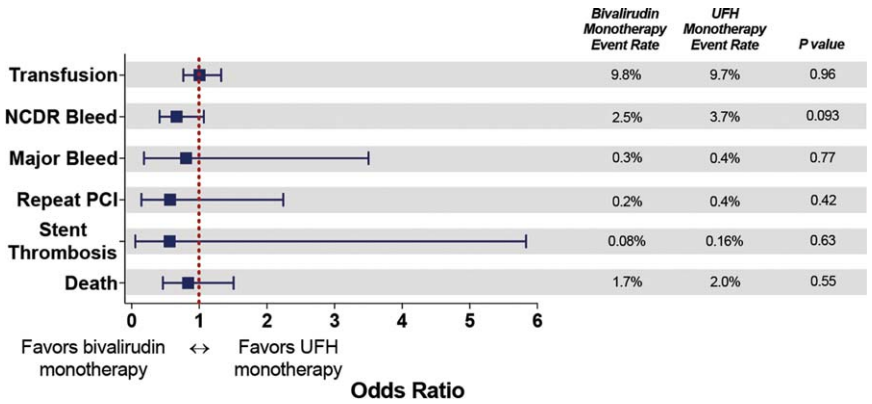

Fig. 3. Adjusted odds ratios of in-hospital outcomes in the matched cohort. Adjusted odds ratios with 95% confidence intervals displayed. Adjusted bivalirudin and UFH event rates are presented on the right side of the figure. Abbreviations: NCDR, National Cardiovascular Data Registry; PCI, percutaneous coronary intervention; UFH, unfractionated heparin. [Color figure can be viewed at wileyonlinelibrary.com]

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.

ACKNOWLEDGMENTS

The authors are indebted to all the study coordinators, investigators, and patients who participated in the BMC2 registry.

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

Acquisition, analysis, or interpretation of data: Schreiber, Khandelwal, Cannon, LaLonde, Gurm

Drafting of the manuscript: Sukul

Critical revision of the manuscript for important intellectual content: Schreiber, Khandelwal, Cannon, LaLonde, Gurm

Statistical analysis: Seth

Obtained funding: Gurm

Study supervision: Gurm

REFERENCES

1. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, et al. Heart disease and stroke statistics-2016 update: A report from the American Heart Association. Circulation 2016;133: e38–e360.
2. Capodanno D, Angiolillo DJ. Antithrombotic therapy in patients with chronic kidney disease. Circulation 2012;125:2649–2661.
3. Kaw D, Malhotra D. Platelet dysfunction and end-stage renal disease. Semin Dial 2006;19:317–322.
4. Best PJ, Lennon R, Gersh BJ, Ting HH, Rihal CS, Bell MR, Herzog CA, Holmes DR, Jr, Berger PB. Safety of abciximab in patients with chronic renal insufficiency who are undergoing percutaneous coronary interventions. Am Heart J 2003;146:345–350.
5. Best PJ, Lennon R, Ting HH, Bell MR, Rihal CS, Holmes DR, Berger PB. The impact of renal insufficiency on clinical outcomes in patients undergoing percutaneous coronary interventions. J Am Coll Cardiol 2002;39:1113–1119.
6. Bonello L, De Labriolle A, Roy P, Steinberg DH, Okabe T, et al. Impact of optimal medical therapy and revascularization on outcome of patients with chronic kidney disease and on dialysis who presented with acute coronary syndrome. Am J Cardiol 2008;102:535–540.
7. Chew DP, Bhatt DL, Kimball W, Henry TD, Berger P, McCullough PA, Feit F, Bittl JA, Lincoff AM. Bivalirudin provides increasing benefit with decreasing renal function: A meta-analysis of randomized trials. Am J Cardiol 2003;92:919–923.
8. Chew DP, Lincoff AM, Gurm H, Wolski K, Cohen DJ, Henry T, Feit F, Topol EJ, Investigators R. Bivalirudin versus heparin and glycoprotein IIb/IIIa inhibition among patients with renal

impairment undergoing percutaneous coronary intervention (a subanalysis of the REPLACE-2 trial). Am J Cardiol 2005;95: 581–585.
9. Charytan D, Kuntz RE. The exclusion of patients with chronic kidney disease from clinical trials in coronary artery disease. Kidney Int 2006;70:2021–2030.
10. Coca SG, Krumholz HM, Garg AX, Parikh CR. Underrepresentation of renal disease in randomized controlled trials of cardiovascular disease. JAMA 2006;296:1377–1384.
11. Lincoff AM, Bittl JA, Harrington RA, Feit F, Kleiman NS, et al. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. JAMA 2003;289:853–863.
12. Stone GW, Witzenbichler B, Guagliumi G, Peruga JZ, Brodie BR, et al. Bivalirudin during primary PCI in acute myocardial infarction. N Engl J Med 2008;358:2218–2230.
13. Kastrati A, Neumann FJ, Mehilli J, Byrne RA, Iijima R, et al. Bivalirudin versus unfractionated heparin during percutaneous coronary intervention. N Engl J Med 2008;359:688–696.
14. Kastrati A, Neumann FJ, Schulz S, Massberg S, Byrne RA, et al. Abciximab and heparin versus bivalirudin for non-ST-elevation myocardial infarction. N Engl J Med 2011;365:1980–1989.
15. Stone GW, McLaurin BT, Cox DA, Bertrand ME, Lincoff AM, et al. Bivalirudin for patients with acute coronary syndromes. N Engl J Med 2006;355:2203–2216.
16. Han Y, Guo J, Zheng Y, Zang H, Su X, et al. Bivalirudin vs heparin with or without tirofiban during primary percutaneous coronary intervention in acute myocardial infarction: the BRIGHT randomized clinical trial. JAMA 2015;313:1336–1346.
17. Steg PG, van 't Hof A, Hamm CW, Clemmensen P, Lapostolle F, et al. Bivalirudin started during emergency transport for primary PCI. N Engl J Med 2013;369:2207–2217.
18. Valgimigli M, Frigoli E, Leonardi S, Rothenbuhler M, Gagnor A, et al. Bivalirudin or Unfractionated Heparin in Acute Coronary Syndromes. N Engl J Med 2015;373:997–1009.
19. Shahzad A, Kemp I, Mars C, Wilson K, Roome C, et al. Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): an open-label, single centre, randomised controlled trial. Lancet 2014;384:1849–1858.
20. Perdoncin E, Seth M, Dixon S, Cannon L, Khandelwal A, et al. The comparative efficacy of bivalirudin is markedly attenuated by use of radial access: insights from Blue Cross Blue Shield of Michigan Cardiovascular Consortium. Eur Heart J 2016;37:1902–1909.
21. Delhaye C, Maluenda G, Wakabayashi K, Ben-Dor I, Collins SD, et al. Safety and in-hospital outcomes of bivalirudin use in dialysis patients undergoing percutaneous coronary intervention. Am J Cardiol 2010;105:297–301.
22. Tsai TT, Maddox TM, Roe MT, Dai D, Alexander KP, et al. Contraindicated medication use in dialysis patients undergoing percutaneous coronary intervention. JAMA 2009;302:2458–2464.
23. Kline-Rogers E, Share D, Bondie D, Rogers B, Karavite D, et al. Development of a multicenter interventional cardiology database: the Blue Cross Blue Shield of Michigan Cardiovascular Consortium (BMC2) experience. J Interv Cardiol 2002;15:387–392.
24. Moscucci M, Rogers EK, Montoye C, Smith DE, Share D, et al. Association of a continuous quality improvement initiative with practice and outcome variations of contemporary percutaneous coronary interventions. Circulation 2006;113:814–822.
25. NCDR CathPCI Registry v4.4 Coder's Data Dictionary. Available at: https://www.ncdr.com/WebNCDR/docs/public-data-collection-documents/cathpci_v4_codersdictionary_4-4.pdf?sfvrsn=2. Accessed: July 28, 2016
26. Hansen BB, Klopfer SO. Optimal full matching and related designs via network flows. J Computat Graph Stat 2006;15:609–627.
27. Gu XS, Rosenbaum PR. Comparison of multivariate matching methods: Structures, distances, and algorithms. J Computat Graph Statist 1993;2:405–420.
28. Development Core Team R. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2015.
29. Mehran R, Nikolsky E, Lansky AJ, Kirtane AJ, Kim YH, et al. Impact of chronic kidney disease on early (30-day) and late (1-year) outcomes of patients with acute coronary syndromes treated with alternative antithrombotic treatment strategies: An ACUITY (Acute Catheterization and Urgent Intervention Triage strategY) substudy. JACC Cardiovasc Interv 2009;2:748–757.
30. Perdoncin E, Zhang M, Riba A, LaLonde TA, Grines CL, Gurm HS. Impact of worsening renal dysfunction on the comparative efficacy of bivalirudin and platelet glycoprotein IIb/IIIa inhibitors: insights from Blue Cross Blue Shield of Michigan Cardiovascular Consortium. Circ Cardiovasc Interv 2013;6:688–693.
31. Cavender MA, Sabatine MS. Bivalirudin versus heparin in patients planned for percutaneous coronary intervention: A meta-analysis of randomised controlled trials. Lancet 2014;384:599–606.
32. Briguori C, Visconti G, Focaccio A, Donahue M, Golia B, Selvetella L, Ricciardelli B. Novel approaches for preventing or limiting events (Naples) III trial: randomized comparison of bivalirudin versus unfractionated heparin in patients at increased risk of bleeding undergoing transfemoral elective coronary stenting. JACC Cardiovasc Interv 2015;8:414–423.
33. Angiomax(R) (bivalirudin): Full Prescribing Information. Available at: http://www.angiomax.com/downloads/Angiomax_US_PI_June_2013.pdf. Accessed: August 13, 2016
34. Amin AP, Marso SP, Rao SV, Messenger J, Chan PS, House J, Kennedy K, Robertus K, Cohen DJ, Mahoney EM. Cost-effectiveness of targeting patients undergoing percutaneous coronary intervention for therapy with bivalirudin versus heparin monotherapy according to predicted risk of bleeding. Circ Cardiovasc Qual Outcomes 2010;3:358–365.
35. Share DA, Campbell DA, Birkmeyer N, Prager RL, Gurm HS, Moscucci M, Udow-Phillips M, Birkmeyer JD. How a regional collaborative of hospitals and physicians in Michigan cut costs and improved the quality of care. Health Aff (Millwood) 2011; 30:636–645.