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Bivalirudin in patients undergoing percutaneous coronary intervention and independent predictors of postoperative adverse events in these patients

A real world retrospective study

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Abstract

The efficacy and safety of bivalirudin in percutaneous coronary intervention (PCI) has always been a hot topic in perioperative antithrombotic therapy, but there are still some controversies. So studies are needed to provide more evidence, especially the real world study which includes patients excluded from previous RCT studys. Our study aimed to investigate these information and analyze the independent predictors of postoperative adverse events.

A retrospective study enrolled 1416 patients underwent PCI in Tianjin Chest Hospital from May 2016 to October 2017. The incidence of stent-thrombosis and net clinical adverse events, including all-cause death, myocardial infarction, stroke, urgent target-vessel revascularization and bleeding, were followed up for 30 days and 1 year. Logistic regression and COX regression were respectively used to analyze independent predictors of bleeding events within 30-days, and independent predictors of Major adverse cardiovascular and cerebrovascular events (MACCE) in patients with stent implantation within 1-year.

Seven hundred six patients were treated with bivalirudin while 710 with unfractionated heparin (UFH). The proportions of diabetes, hypertension, anemia, myocardial-infarction history, PCI history, moderate-to-severe renal-impairment, gastrointestinal-bleeding history in the bivalirudin group were significantly higher ($P < .05$). Women, anemia were independent risk factors for bleeding within 30-days ($P < .05$). Among 682 patients with stent implantation in bivalirudin group, anemia, Body Mass Index (BMI) $>25\,kg/m^2$, KILLIP ≥ 2, ejection fraction (EF) $<45\%$, eGFR <60 ml/minutes were independent risk factors for MACCE, while Statins, proton pump inhibitor (PPI) were independent protective factors for MACCE with-in 1-year ($P < .05$).

Bivalirudin have good anticoagulant effect and lower bleeding risk during PCI, especially in patients with higher bleeding risk. In patients treated with bivalirudin, female, anemia were independent predictors of bleeding within 30-days, BMI $>25\,kg/m^2$, anemia, KILLIP ≥ 2, EF $<45\%$, eGFR <60 ml/minutes were independent risk factors and Statins, PPI were independent protective factors of MACCE within 1-year.

Abbreviations: ACS = acute coronary syndrome, ACT = activation of coagulation time, EF = ejection fraction, MACCE = Major adverse cardiovascular and cerebrovascular events, PCI = percutaneous coronary intervention, PPI = proton pump inhibitor, UFH = unfractionated heparin.

Keywords: bivalirudin, coronary artery disease, percutaneous coronary intervention, real world research

1. Introduction

Percutaneous coronary intervention is a common and safe treatment for coronary heart disease aiming to revascularization. During PCI, the coagulation system is activated by invasive surgical instruments, intimal tear at lesion site, exposure of plaque content, and stent implantation itself. Especially in acute

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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myocardial infarction, platelet and coagulation system have been activated before PCI, because of plaque rupture or plaque surface erosion.[1,2] Therefore, anticoagulation therapy is used in PCI to reduce the risk of thrombosis and embolism.

Bivalirudin is a synthetic direct thrombin inhibitor. Its characteristics are as follows:

1. Drug concentration peaks in about 5 minutes and has a sustained and stable anticoagulant effect compared to UFH.
2. The excretion of bivalirudin is not affected in patients with mild renal impairment and there is no need for dosage reduction.
3. Bivalirudin does not interact with platelet factor IV, which in turn induces Heparin-induced thrombocytopenia. Therefore, bivalirudin is an ideal substitute for heparin drugs in patients with a history of Heparin-induced thrombocytopenia.
4. The anticoagulant effect of bivalirudin does not depend on plasma factors such as antithrombin III, and its amino terminus can directly bind to thrombin, thereby exerting anticoagulant effect.

It is important to note that bivalirudin has an inhibitory effect on both thrombin in the thrombus and free thrombin in the circulation. In acute myocardial infarction patients with heavier thrombus load, bivalirudin may play a better role than other anticoagulant drugs.

Previous Evidence-based medicine research suggests that bivalirudin can reduce the risk of bleeding after PCI, and there is no difference in ischemic events between bivalirudin and UFH.[3,4] 2018 ESC/EACTS guidelines on myocardial revascularization suggests bivalirudin routine use as a class IIb recommendation in patients with acute coronary syndrome (ACS) and points out that previous studies have overestimated the benefits of reduced bleeding risk from bivalirudin.[5] The discussion on the effectiveness and safety of bivalirudin was once again initiated. Therefore, this study was conducted to investigate the effectiveness and safety of bivalirudin in patients with coronary heart disease in the real world, and to analyze the independent predictors of bleeding events within 30 days and MACCE within 1 year.

2. Methods

A retrospective study was conducted on 1416 patients with coronary heart disease underwent PCI in Tianjin Chest Hospital from May 2016 to October 2017. The study protocol was approved by the Research Ethics Committee of Tianjin Chest Hospital on human research (2018LW-005).

2.1. Enrollment criteria

Patients with coronary heart disease underwent PCI in Tianjin Chest Hospital from May 2016 to October 2017 were enrolled in this study.

Inclusion criteria: ACS patients underwent PCI, including:

1. myocardial infarction which sub-divided into ST-segment elevation myocardial infarction and non-ST-segment elevation myocardial infarction, defined as: acute myocardial injury with clinical evidence of acute myocardial ischemia and with detection of a rise and/or fall of cardiac troponin values with at least 1 value above the 99th percentile Upper reference limit and at least one of the following:
    1. Symptoms of myocardial ischemia;
    2. New ischemic ECG changes;
    3. Development of pathological Q waves;
    4. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology;
    5. Identification of a coronary thrombus by angiography or autopsy.[6]
    6. Unstable angina, defined as myocardial ischemia at rest or minimal exertion in the absence of cardiomyocyte necrosis.[7]

Exclusion criteria:

1. After primary PCI, the continuous application time of bivalirudin is less than 4 hours or the dosage is insufficient;
2. the data are incomplete;
3. the expected survival time is less than 1 year, such as the diagnosis of malignant tumors.

Patients treated with Bivalirudin (Salubris Pharmaceuticals Co) was given as a bolus of 0.75 mg/kg followed by infusion of 1.75 mg/kg/hour during the PCI procedure and for 4 hours afterwards. Activation of coagulation time (ACT) was detected 5 minutes after loading dose. If ACT was less than 225 second, 0.30 mg/kg of bivalirudin was added. The UFH group was given intravenous injection of UFH 80-100 U/kg, and the dosage was adjusted according to ACT results. Double anti-platelet drugs were given routinely before operation. Because of prasugrel is not listed in China, so this study did not use this drug, ticagrelor or clopidogrel were selected as P2Y12 inhibitors. Both radial and femoral artery approaches can be included in this study.

2.2. Data collection

The clinical baseline data, surgical treatment information, perioperative antithrombotic treatment and other data of the selected patients in this study were extracted according to the original hospitalized medical records. The occurrence of adverse events within 30 days and 1 year after surgery was completed by telephone follow-up or subsequent visit. The deadline for follow-up was 2018.10.

2.3. Outcome measurements

Effective outcomes of this study was the rate of adverse clinical events at 30 days and 1year, including all-cause death, reinfarction, ischemia-driven target vessel revascularization, stroke and stent thrombosis. Safety outcomes was the rate of bleeding events as defined by the Bleeding Academic Research Consortium definition (grades 1–5).[8]

2.4. Statistical analysis

Statistical analysis was performed using SPSS 19.0 software (IBM, New York, USA). Continuous variables are tested for normality. If they conform to normal distribution, they are expressed by mean ± standard deviation ($\bar{x} \pm s$). T test is used for comparison between the 2 groups. If they do not conform to normal distribution, they are expressed by median (range) and non-parametric test is used for comparison between the 2 groups. The count data is expressed as a percentage, and the χ^2 test or Fisher exact test is used for comparison between the 2 groups. $P < .05$ was considered statistically significant. Logistic regression analysis models were used for statistical analysis of independent predictors of bleeding events within 30 days. The independent

predictors of MACCE events within 1 year after stent implantation were statistically analyzed using the COX regression analysis model. And Influencing factors of $P < .1$ were introduced into regression model in each single factor analysis.

3. Results

3.1. Baseline characteristics and Clinical outcome

In this study, 706 patients were enrolled in bivalirudin group and 710 patients were enrolled in UFH group. Patients in bivalirudin group has higher average age (70.1 ± 11.1 vs 57.4 ± 10.9 years, $P < .001$) and lower Proportion of male patients (59.8% vs 85.1%, $P < .001$). Meanwhile, patients with higher comorbidities than those in the UFH group. Some of these complications can increase the risk of bleeding. As expected, the Crusade score was higher in bivalirudin group (35.2 ± 14.6 vs 20.5 ± 15.4, $P < .001$). And the proportion of patients with moderate to high risk of bleeding (CRUSADE score >30 points) was as high as 64%. According to The Academic Research Consortium for High Bleeding Risk (ARC-HBR),[9] 45% (318/706)patients in bivalirudin group are at high bleeding risk (Table 1). P2Y12 inhibitors including clopidogrel and Ticagrelor were used before PCI. In the 2 groups, the proportion of clopidogrel load of 600 mg in the bivalirudin group was higher, and the difference was statistically significant ($P < .05$). When patients discharge, the proportion of aspirin and statins use in UFH group was significantly higher than that in the bivalirudin group ($P < .05$). There was no significant difference in other medications between the 2 groups. The proportion of patients with multiple vascular lesions and right coronary lesions in bivalirudin group was significantly higher than that in UFH group, and the proportion of patients with anterior descending branch lesions was significantly lower than that in UFH group. ($P < .05$) (Table 1).

It can be seen that almost half patients use bivalirudin in this study have a higher risk of bleeding according to ARC-HBR. In this condition, there was no significant increase in MACCE, bleeding events and stent thrombosis compared with UFH. These results suggest that bivalirudin is effective and safe, especially in patients at high bleeding risk (Table 1).

3.2. Independent predictors of bleeding events within 30 days

During a follow-up of 30 days, 16 of 706 patients developed bleeding events with an incidence of 2.3%. After comparing the clinical data of the bleeding group and the no-bleeding group, factors of difference between the 2 groups were included in the multivariate regression analysis: primary PCI, age >75 years, female, BMI, eGFR <60 ml/minutes, anemia, stent implantation. The results showed women (OR: 8.954, 95% CI: 1.885–42.528, $P = .006$), anemia (OR: 4.746, 95% CI: 1.407–16.000, $P = .012$) were independent risk factors for bleeding events (Tables 2 and 3).

3.3. Independent predictor of MACCE events in patients with stent implantation

A follow-up of 1 year found that a total of 682 patients with stent implantation had MACCE in 36 patients, an incidence of 5.3%. After comparing the clinical data of the MACCE group and the no-MACCE group, factors of difference between the 2 groups were included in the multivariate regression analysis: primary PCI, age >75 years, female, stroke history, BMI >25 kg/m^2, radial artery approach, eGFR <60 ml/minutes, application of statins, application of Proton pump inhibitor (PPI) drugs, Anemia, KILLIP ≥2, multiple vascular lesions, ejection fraction (EF) value <45%. The results showed: BMI >25 kg/m^2 (OR: 3.332, 95% CI: 1.201–9.246, $P = .021$), KILLIP ≥2 (OR: 2.147, 95% CI: 1.067–4.320, $P = .032$), anemia (OR: 2.074, 95% CI: 1.009–4.265, $P = .047$), EF value <45% (OR: 4.043, 95% CI: 1.789–9.136, $P = .001$), eGFR <60 ml/minutes (OR: 6.795, 95% CI: 2.345–19.686, $P < .001$) were independent risk factors for MACCE events. Statins (OR: 0.106, 95% CI: 0.049–0.230, $P < .001$), PPIs (OR: 0.421, 95% CI: 0.194–0.914, $P = .029$) were independent protective factors for MACCE events (Tables 4 and 5, Fig. 1).

4. Discussion

Since the introduction of bivalirudin, its efficacy and safety in PCI have been compared with UFH constantly. In stable angina and ACS patients who undergoing elective PCI, the anti-ischemic effect of bivalirudin is similar to that of UFH.[10–13] Whether bivalirudin increase the risk of acute stent thrombosis in patients undergoing primary PCI has reached a conclusion mostly. Since the publication of the BRIGHT study, the MATRIX study, and the VALIDATE-SWEDEHEART study,[3,4,14] the concept of the empty window of antithrombotic therapy in primary PCI, it has been clarified that bivalirudin, with the high-dose delayed application method after PCI, does not increase the risk of acute stent thrombosis. It is consistent with the results of this study.

The ESC/EACTS 2018 myocardial revascularization Guideline suggest bivalirudin as a Class IIb recommendation for ACS patients, and UFH remains the preferred drug. The guideline refer to the VALIDATE-SWEDEHEART study,[14] which under the conditions of the radial artery approach and limited the application of platelet IIb/IIIa receptor antagonists, concluded that the 2 drugs had similar risk of ischemia and hemorrhage. At the same time, some meta-analysis results suggest that the benefit of bivalirudin in reducing bleeding risk is associated with higher Glycoprotein platelet inhibitor application in heparin group.[15–17] Therefore, the current focus on bivalirudin is mainly on whether bivalirudin can reduce the risk of bleeding.

In 2019, The Academic Research Consortium defined the concept of patients at HBR undergoing percutaneous coronary intervention. The definition is intended to provide consistency in defining this population for clinical trials and to complement clinical decision-making and regulatory review. Patients are considered to be at HBR if at least 1 major or 2 minor criteria are met.[9] In our study, 25% (180/706) patients in bivalirudin group have 1 major criterion (Oral Anticoagulation, Anemia, eGFR <30 ml/minutes, Cirrhosis With Portal Hypertension, intracerebral hemorrhage), and 20%(138/706) patients have 2 minor criterions (age ≥75 years, eGFR <60 ml/minutes, Previous Ischemic Stroke), which is significantly higher than UFH group. And previous studies had shown that, as the number of bleeding determinants increased, the risk of bleeding will increase.[18] But our study showed that the risk of bleeding was similar between the bivalirudin group and the heparin group. So this study suggested that bivalirudin can reduce the risk of bleeding in patients at high bleeding risk. Indirectly, we can draw a conclusion, bivalirudin has a lower risk of bleeding than UFH. This is consistent with the BRIGHT study, which also balanced

Table 1

Characteristics and clinical events of patients treated with UFH and bivalirudin.

Characteristic	Bivalirudin (n = 706)	UFH (n = 710)	*P* value
Age, years	70.1 ± 11.1	57.4 ± 10.9	<.001
Male (%)	422 (59.8)	604 (85.1)	<.001
Body mass, kg	65.9 ± 11.2	71.8 ± 11.0	.353
BMI (kg/m^2)	23.8 ± 1.7	25.5 ± 3.5	.306
Diagnosis (%)			
STEMI	330 (46.7)	327 (46.1)	.796
NSTEMI	132 (18.7)	100 (14.1)	.851
UA	244 (34.6)	283 (39.9)	.039
Medical history (%)			
Diabetes	236 (33.4)	164 (23.1)	<.001
Hypertension	488 (69.1)	277 (39.0)	<.001
Hyperlipidemia	232 (32.9)	250 (35.2)	.351
Smoker	302 (42.8)	454 (63.9)	<.001
MI	60 (8.5)	21 (2.9)	<.001
PCI	96 (13.6)	36 (5.0)	<.001
Stroke	238 (33.7)	64 (9.0)	<.001
Gastrointestinal bleeding	40 (5.7)	14 (2.0)	<.001
Retinal hemorrhage	8 (1.1)	4 (0.6)	.242
Peptic ulcer	14 (2.0)	6 (0.8)	.070
KILLIP class ≥2 (%)	288 (40.8)	109 (15.4)	<.001
Anemia # (%)	228 (32.3)	39 (5.5)	<.001
Hemoglobin	128.5 ± 17.1	136.5 ± 18.1	.032
Platelet count	209.4 ± 59.0	207.4 ± 39.0	.186
eGFR	71.7 ± 29.7	95.7 ± 40.7	.012
eGFR <60 ml/minutes	278 (39.4)	62 (8.7)	<.001
EF value (%)	52.6 ± 8.9	51.4 ± 9.5	.357
CRUSADE score	35.2 ± 14.6	20.5 ± 15.4	<.001
CRUSADE score >30 points	452 (64.0)	106 (14.9)	<.001
ARC-HBR	318 (45)	88 (12.4)	<.001
Aspirin load (%)	294 (41.6)	288 (40.1)	.680
Clopidogrel load (%)	128 (18.1)	130 (18.3)	.930
Loading dose (%)			
300 mg	102 (79.7)	110 (84.6)	<.001
600mg	26 (20.3)	20 (15.4)	<.001
Ticagrelor load (%)	166 (23.5)	158 (22.3)	.573
Tirofiban (%)	56 (7.9)	48 (6.8)	.398
Oral anticoagulant (%)	12 (1.7)	9 (1.3)	.501
Warfarin	8 (1.1)	4 (0.6)	.242
NOAC	4 (0.6)	5 (0.7)	.745
Medications at discharge (%)			
Aspirin	658 (93.2)	688 (96.9)	.001
Clopidogrel	602 (85.3)	588 (82.8)	.208
Ticagrelor	86 (12.2)	115 (16.2)	.030
Statins	670 (94.9)	698 (98.3)	<.001
Beta-blocker	530 (75.1)	523 (73.7)	.544
CCB	126 (17.8)	130 (18.3)	.821
ACEI/ARB	446 (63.2)	460 (64.8)	.527
PPI	578 (81.9)	565 (79.6)	.274
Arterial access (%)			
Transradial	434 (61.5)	460 (64.8)	.196
Transfemoral	272 (38.5)	250 (35.2)	.196
Multivessel disease	628 (89.0)	489 (68.9)	<.001
Revascularization strategy (%)			
medical therapy only	4 (0.6)	3 (0.4)	.699
CABG	2 (0.3)	2 (0.3)	.995
PTCA	16 (2.3)	18 (2.5)	.741
STENT	684 (96.9)	687 (96.7)	.895
Drug-eluting stent type (%)			
Zotarolimus-eluting	32/888 (3.6)	38/868 (4.4)	.407
Everolimus-eluting	130/888 (14.6)	145/868 (16.7)	.234
Sirolimus-eluting	726/888 (81.8)	685/86 (78.9)	.134
Culprit vessel treated with PCI (%)			
Left main coronary artery	22 (3.1)	24 (3.4)	.779
LAD coronary artery	304 (43.1)	340 (47.9)	<.001
LCX coronary artery	118 (16.7)	110 (15.5)	.021
Right coronary artery	272 (38.5)	236 (33.2)	.038
Graft vessel	8 (1.1)	5 (0.7)	.078
Mean culprit lesion RVD, (mm)	3.06 ± 0.52	3.07 ± 0.58	.402
Number of stents per patient	1.26 ± 0.56	1.20 ± 0.59	.047
Mean stent length, mm	32.8 ± 18.4	32.9 ± 17.7	.841
Thrombus aspiration (%)	108 (15.3)	108 (15.2)	.964
TIMI flow			
Pre-PCI (%)			
0–1	274 (38.8)	265 (37.3)	.565
2	80 (11.3)	70 (9.9)	.368
3	348 (49.3)	375 (52.8)	.185
PostPCI (%)			
0–1	2 (0.3)	3 (0.4)	.659
2	0	0	NC
3	704 (99.7)	707 (99.6)	.659
30-day outcomes			
MACE	30 (4.2)	42 (5.9)	.154
MACCE	16 (2.3)	18 (2.5)	.741
All-cause death	16 (2.3)	9 (1.1)	.154
Cardiac death	12 (1.7)	8 (1.2)	.361
reinfarction	0	3 (0.4)	.250
stroke	2 (0.3)	4 (0.6)	.688
Ischemic TVR	0	6 (0.8)	.041
All bleeding	16 (2.3)	24 (3.4)	.206
BARC 2	6 (0.8)	9 (1.3)	.443
BARC3–5	2 (0.3)	4 (0.6)	.688
Acquired thrombocytopenia	0	1 (0.1)	1.000
Stent thrombosis	0	2 (0.3)	.482
definite	0	2 (0.3)	.482
probable	0	0	NC
Acute (<24 hours)	0	2 (0.3)	.482
Subacute (1–30 days)	0	0	NC
1-year outcomes			
MACE	46 (6.5)	53 (7.5)	.484
MACCE	24 (3.4)	30 (4.2)	.417
All-cause death	20 (2.8)	14 (2.0)	.290
Cardiac death	16 (2.3)	12 (1.7)	.436
reinfarction	10 (1.4)	11 (1.5)	.836
stroke	6 (0.8)	4 (0.6)	.744
Ischemic TVR	2 (0.3)	3 (0.4)	1.000
All bleeding	22 (3.1)	23 (3.2)	.895
BARC 2	10 (1.4)	12 (1.7)	.677
BARC3-5	8 (1.1)	6 (0.8)	.584
Acquired thrombocytopenia	0	0	NC
Stent thrombosis	6 (0.8)	4 (0.6)	.744
definite	0	0	NC
probable	6 (0.8)	4 (0.6)	.744

ACEI = angiotensin-converting enzyme inhibitor, Anemia = defined as male hemoglobin <120 g/L, female <110 g/L, ARB = angiotensin receptor blockers, ARC-HBR = the Academic Research Consortium for High Bleeding Risk, BMI = Body Mass Index, CABG = coronary artery bypass grafting, CCB = calcium channel blockers, CRUSADE = Can Rapid risk stratification of Unstable angina patients Suppress Adverse outcomes with Early implementation of the ACC/AHA guidelines, EF = ejection fraction, eGFR = estimated glomerular filtration rate, Ischemic TVR = ischemic target vessel reconstruction, LAD coronary artery = left anterior descending branch coronary artery, LCX coronary artery = left circumflex branch coronary artery, MACCE = major adverse cardiovascular and cerebrovascular events, MACE = major adverse cardiovascular events, MI = myocardial infarction, NC = no computed data, NOAC = new oral anticoagulant, NSTEMI = non-ST-segment elevation myocardial infarction, PCI = percutaneous coronary intervention, Post-PCI = post- percutaneous coronary intervention, PPI = proton pump inhibitor, Pre-PCI = pre- percutaneous coronary intervention, PTCA = percutaneous transluminal coronary angioplasty, STEMI = ST-segment elevation myocardial infarction, UA = unstable angina.

Table 2

Characteristics of bleeding group and no-bleeding group.

characteristic	Bleeding group (n = 16)	No bleeding group (n = 80)	*P* value
Age, years	81.3 ± 4.4	69.8 ± 11.0	<.001
>75 years (%)	12 (75.0)	31 (38.7)	.003
female (%)	14 (87.5)	32 (40.0)	<.001
Body mass, kg	64.4 ± 10.5	69.6 ± 11.2	.063
BMI (kg/m^2)	22.8 ± 1.3	23.8 ± 1.7	.014
Primary PCI	10 (62.5)	33 (41.3)	.096
STEMI	10 (62.5)	37 (46.3)	.201
Medical history (%)			
Diabetes	4 (25.0)	27 (33.8)	.470
Hypertension	12 (75.0)	55 (68.7)	.607
Hyperlipidemia	4 (25.0)	26 (32.5)	.498
Smoker	10 (62.5)	34 (42.5)	.107
MI	16 (100)	7 (8.7)	<.001
PCI	2 (12.5)	11 (13.7)	.897
Stroke	8 (50.0)	27 (33.7)	.163
Gastrointestinal bleeding	0 (0)	5 (6.3)	.321
Retinal hemorrhage	0 (0)	1 (1.3)	1.000
KILLIP class ≥2 (%)	4 (25.0)	33 (41.2)	.194
Anemia (%)	12 (75.0)	25 (31.3)	<.001
Hemoglobin	109.1 ± 21.8	128.9 ± 16.7	<.001
Platelet count	222.4 ± 54.6	209.1 ± 59.1	.376
eGFR	48.5 ± 25.0	72.4 ± 29.6	.001
eGFR <60 ml/minutes	12 (75.0)	31 (38.8)	.003
EF value (%)	51.9 ± 7.0	52.6 ± 9.0	.740
CRUSADE Score	47.9 ± 16.4	34.9 ± 14.40	<.001
CRUSADE score>30 points	14 (87.5)	51 (63.8)	.050
Aspirin load (%)	10 (62.5)	33 (41.2)	.087
Clopidogrel load (%)	4 (25.0)	14 (17.5)	.471
Loading dose (%)			
300 mg	4 (100)	11 (78.5)	.693
600 mg	0 (0)	3 (21.4)	.693
Ticagrelor load (%)	6 (37.5)	19 (23.8)	.182
Tirofiban (%)	2 (12.5)	6 (7.5)	.494
Medications at discharge (%)			
Aspirin	16 (100)	74 (92.5)	.274
Clopidogrel	16 (0)	68 (85.0)	.093
Ticagrelor	0 (0)	10 (12.5)	.132
Statins	16 (100)	76 (95.0)	.717
Beta-blocker	10 (62.5)	60 (75.0)	.240
CCB	4 (25.0)	14 (17.5)	.450
ACEI/ARB	8 (50.0)	51 (63.8)	.269
PPI	14 (87.5)	65 (81.3)	.554
Arterial access (%)			
Transradial	8 (50.0)	49 (61.3)	.340
Multivessel disease	14 (87.5)	71 (88.8)	.821
Revascularization strategy (%)			
medical therapy only	0 (0)	0 (0)	NC
CABG	0 (0)	1 (1.2)	1.000
PTCA	2 (12.5)	2 (2.5)	.053
STENT	14 (87.5)	77 (96.2)	.042
Thrombus aspiration (%)	4 (25.0)	12 (15.0)	.275

ACEI = angiotensin-converting enzyme inhibitor, Anemia = defined as male hemoglobin <120 g/L, female <110 g/L, ARB = angiotensin receptor blockers, BMI = Body Mass Index, CABG = coronary artery bypass grafting, CCB = calcium channel blockers, CRUSADE = Can Rapid risk stratification of Unstable angina patients Suppress Adverse utcomes with Early implementation of the ACC/AHA guidelines, EF = ejection fraction, eGFR = estimated glomerular filtration rate, MI = myocardial infarction, PCI = percutaneous coronary intervention, PPI = proton pump inhibitor, PTCA = percutaneous transluminal coronary angioplasty, STEMI = ST-segment elevation myocardial infarction.

Table 3

Multivariate analysis of independent predictors of bleeding events within 30 days.

Analysis factor	OR	95% CI	*P* value
Primary PCI	1.349	0.409–4.454	.623
Age >75years	2.341	0.610–8.978	.215
Female	8.954	1.885–42.528	.006
BMI	1.002	0.708–1.418	.993
eGFR<60 ml/minutes	1.787	0.472–6.766	.393
Anemia	4.746	1.407–16.000	.012
Stent implantation	1.041	0.185–5.851	.092

Anemia = defined as male hemoglobin <120 g/L, female <110 g/L, BMI = Body Mass Index, eGFR = estimated glomerular filtration rate, PCI = percutaneous coronary intervention.

radial artery approach and glycoprotein platelet inhibitor application.

In this study, multivariate logistic regression analysis found that women and anemia were independent risk factors for bleeding within 30 days after PCI in patients applied bivalirudin. The traditional bleeding risk factors of advanced age and renal dysfunction (eGFR <60 ml/minutes) are no longer independent risk factors for bleeding events in patients applying bivalirudin.[19] This suggests that bivalirudin can reduce the risk of bleeding in these patients. Another study about bleeding predictors in patients with bivalirudin showed that renal dysfunction was an independent risk factor for clinically significant bleeding events in bivalirudin, but this effect was only present in patients with eGFR <30 ml/minutes.[20] The above conclusions are considered to be related to the lower ratio of renal excretion of bivalirudin and the lower risk of drug accumulation due to decreased renal function.

Previous studies have shown that the use of bivalirudin during PCI in women can reduce the risk of major bleeding by 44% and significantly reduce the risk of death.[21] However, this study shows that women remain an independent risk factor for bleeding. In fact, the female patients with bleeding events were mostly hematoma at the puncture site, and only 4 patients with severe bleeding (melena, cerebral hemorrhage). Therefore, it is suggested that the increased risk of bleeding in females may be associated with a higher risk of puncture-related bleeding. Studies have reported that the incidence of hematoma at the puncture site of females is still significantly higher than that of men when the radial artery approach is taken, but there is no gender difference in the incidence of major bleeding events,[22] supporting the view of this study. The increased risk of puncture-related bleeding in women is considered to be related to the following factors:

1. Women with coronary heart disease are older, with lower body weight, and have increased vascular fragility.[23]
2. Female patients have smaller radial arteries with a higher risk of intraoperative injury. Studies by Optical coherence tomography observed that 67.1% patients with radial artery sheath placement occurring intimal dissection, and 35.6% patients with media tear.[24] It can be seen that the risk of injury to the access vessel is high due to sheath placement and surgical procedures.
3. The risk of radial artery spasm in women is 3 times higher than that in male patients,[25] so the risk of radial artery injury is higher in females.

Therefore, when the female patients undergoing PCI, it should first be gentle and avoid violent operation to reduce the risk of

Table 4

Characteristics of MACCE group and no MACCE group.

characteristic	MACCE group (n = 36)	No MACCE group (n = 160)	*P* value
Age, years	79.1 ± 7.3	69.26 ± 10.9	<.001
>75 years (%)	28 (77.8)	56 (35.0)	<.001
female (%)	20 (55.6)	61 (38.1)	.036
Body mass, kg	64.5 ± 9.8	70.0 ± 11.1	.004
BMI (kg/m^2)	23.3 ± 1.7	23.8 ± 1.6	.037
BMI>25 kg/m^2 (%)	8 (22.2)	41 (25.6)	.670
Primary PCI	24 (66.7)	62 (38.8)	.001
STEMI	20 (55.6)	71 (44.4)	.198
Medical history (%)			
Diabetes	14 (38.9)	52 (32.5)	.451
Hypertension	26 (72.2)	110 (68.8)	.687
Hyperlipidemia	10 (27.8)	53 (33.1)	.483
Smoker	16 (44.4)	68 (42.5)	.839
MI	4 (11.1)	13 (8.1)	.515
PCI	8 (22.2)	21 (13.1)	.115
Stroke	6 (16.7)	56 (35)	.026
Gastrointestinal bleeding	10 (27.8)	7 (4.4)	<.001
Retinal hemorrhage	0 (0)	2 (1.2)	1.000
KILLIP class ≥2 (%)	20 (55.6)	65 (40.6)	.082
Anemia (%)	24 (66.7)	48 (30.0)	<.001
Hemoglobin	116.9 ± 22.2	129.7 ± 16.1	.002
Platelet count	214.4 ± 48.3	210.1 ± 61.5	.678
eGFR	40.9 ± 13.8	74.6 ± 29.2	<.001
eGFR <60 ml/minutes	32 (88.9)	56 (35.0)	<.001
EF value (%)	41.8 ± 11.3	53.4 ± 8.3	<.001
EF value <45% (%)	22 (61.1)	27 (16.9)	<.001
CRUSADE Score	52.9 ± 11.7	33.5 ± 13.7	<.001
CRUSADE Score >30points	34 (94.4)	98 (61.3)	<.001
Aspirin load (%)	22 (61.0)	62 (38.7)	.008
Clopidogrel load (%)	12 (33.3)	26 (16.3)	.007
Ticagrelor load (%)	10 (27.8)	37 (23.1)	.500
Tirofiban (%)	2 (5.6)	12 (7.5)	.631
Medications at discharge (%)			
Aspirin	24 (92.3)	154 (96.3)	.359
Clopidogrel	22 (84.6)	140 (87.5)	.650
Ticagrelor	4 (15.4)	20 (12.5)	.650
Statins	22 (84.6)	156 (97.5)	.001
Beta-blocker	18 (69.2)	123 (76.8)	.373
CCB	2 (7.7)	29 (18.1)	.168
ACEI/ARB	16 (61.5)	104 (65.0)	.741
PPI	18 (69.2)	135 (84.4)	.043
Arterial access (%)			
Transradial	14 (38.9)	104 (65.0)	.002
Multivessel disease	34 (94.4)	141 (88.1)	.029
Culprit vessel treated with PCI (%)			
LM	2 (5.6)	4 (2.5)	.338
LAD	16 (44.4)	71 (44.4)	.984
LCX	4 (11.1)	28 (17.5)	.333
RCA	16 (44.4)	59 (36.9)	.358
Thrombus aspiration (%)	6 (16.7)	24 (15.0)	.767
TIMI flow (%)			
Pre-PCI			
0–1	18 (50%)	59 (36.9)	.113
2	2 (5.6)	19 (11.9)	.237
3	16 (44.4)	82 (51.3)	.438

ACEI = angiotensin-converting enzyme inhibitor, Anemia = defined as male hemoglobin <120 g/L, female <110 g/L, ARB = angiotensin receptor blockers, BMI = Body Mass Index, CCB = calcium channel blockers, CRUSADE = Can Rapid risk stratification of Unstable angina patients Suppress Adverse outcomes with Early implementation of the ACC/AHA guidelines, EF = ejection fraction, eGFR = estimated glomerular filtration rate, LAD coronary artery = left anterior descending branch coronary artery, LCX coronary artery = left circumflex branch coronary artery, LM = left main coronary artery, MI = myocardial infarction, PCI = percutaneous coronary intervention, PPI = proton pump inhibitor, RCA = right coronary artery, STEMI = ST-segment elevation myocardial infarction.

Table 5

Independent predictive factors of MACCE within 1 year.

Analysis factor	HR	95% CI	*P* value
Primary PCI	1.401	0.351–5.590	.633
female	2.021	0.993–4.110	.052
Age >75 years	1.619	0.654–4.007	.297
BMI>25 kg/m^2	3.332	1.201–9.246	.021
Stroke	0.764	0.332–1.760	.528
Transradial	0.844	0.234–3.050	.796
KILLIP class ≥2	2.147	1.067–4.320	.032
Multivessel disease	1.808	0.351–9.303	.479
Statins	0.106	0.049–0.230	<.001
PPI	0.421	0.194–0.914	.029
Anemia	2.074	1.009–4.265	.047
EF value <45%	4.043	1.789–9.136	.001
eGFR<60 ml/minutes	6.795	2.345–19.686	<.001

Anemia = defined as male hemoglobin <120 g/L, female <110 g/L, BMI = Body Mass Index, EF = ejection fraction, eGFR = estimated glomerular filtration rate, PCI = percutaneous coronary intervention, PPI = proton pump inhibitor.

hematoma at the puncture site, especially in patients with arteriosclerosis, small blood vessels, and anxiety. Secondly, considering that female patients are mostly elder and have multiple comorbidities, the bleeding risk is higher than that of male patients, bivalirudin application is a better choice.

Previous studies have shown that patients with anemia have a higher risk of death and major bleeding during 1 year than those without anemia, but there is no significant difference in MACCE, suggesting that the increased risk of death from anemia is mainly due to bleeding risk increases.[26] Subsequently, a subgroup analysis from the ACUITY study showed a significant increase in the ischemic event in anemia patients.[27] In 2015, a meta-analysis included 68,528 patients in 17 clinical studies showed that patients with anemia had a significantly increased ischemic risk, recurrent myocardial infarction, major bleeding, risk of death, and major adverse cardiovascular events.[28] The results of this study are consistent with previous studies. In patients with bivalirudin, anemia is an independent risk factor of MACCE (OR: 2.074, 95% CI: 1.009–4.265, $P = .047$) and bleeding events (OR: 4.746, 95% CI: 1.407–16.000, $P = .012$). The increase in adverse events in anemia patients is related to the following factors:

1. Anemia leads to a decrease in oxygen transport carriers in the body, imbalance in myocardial oxygen supply and demand, and is more pronounced in patients with coronary artery disease with vascular stenosis.
2. Anemia leads to sympathetic excitation, activation of the renin angiotensinaldosterone system.
3. Renin angiotensin aldosterone system, which increases heart rate and blood volume, affecting ventricular remodeling and cardiac function.[29]
4. Most patients with anemia have peptic ulcer, gastrointestinal tumors, vascular disease, renal insufficiency and other diseases, increasing the risk of bleeding.[28]
5. Anemia may reduce thrombosis, decrease platelet function, increase inflammatory factor levels, and increase the risk of bleeding.[29]
6. Patients with severe anemia need to infuse blood products, which may increase the risk of acute renal injury during perioperative PCI,[30] increasing the risk of ischemia and bleeding.

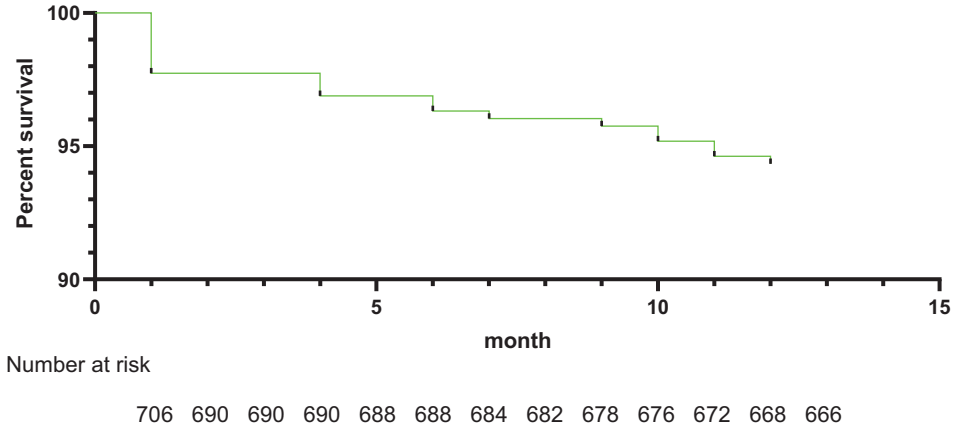

Figure 1. Survival curve of MACCE in patients with bivalirudin.

This study showed that renal dysfunction (eGFR <60 ml/minutes) was an independent risk factor for MACCE after stent implantation (OR: 6.795, 95% CI: 2.345–19.686, $P < .001$), consistent with previous studies. Consider the following factors:

1. Abnormal calcium and phosphorus metabolism in patients with renal insufficiency, leading to decreased vascular compliance, more common calcification lesions, and increased risk during PCI.
2. Renal dysfunction combined with hyperhomocysteinemia, oxidative stress, inflammatory state, accelerate the progression of atherosclerosis.
3. Patients with renal dysfunction often have multiple traditional cardiovascular risk factors, such as hypertension, diabetes, and hyperlipidemia. The superposition of multiple risk factors increases the risk of MACCE.[31]
4. Patients with renal insufficiency have an increased risk of perioperative acute kidney injury, progressive deterioration of renal function may lead to increased circulating load, and increase the risk of adverse cardiac events.

However, considering the benefit of bleeding reduction, in patients with moderate to severe renal injury, bivalirudin should be preferred during PCI.

Decreased LVEF leads to hypercoagulable state, which can directly lead to thromboembolic disease.[32] Especially, the decrease of LVEF leads to coronary blood supply reduction, myocardial ischemia, hypoxia, and increased risk of stent thrombosis. Studies have shown that the risk of Major Adverse Cardiovascular Events and death doubles when patients combine either LVEF <40% or eGFR <60 ml/minutes, and when both factors occur simultaneously, the risk of Major Adverse Cardiovascular Events and death increases 5-folds.[33] This study showed that KILLIP ≥2 and EF <45% were independent risk factors for MACCE events after stent implantation. Therefore, saving cardiac ejection function is essential to improve the patient's short-term and long-term prognosis. In patients with acute myocardial infarction, it is necessary to open the infarct-related blood vessels as early as possible, and to increase the number of myocardial cell survival in the ischemic area as much as possible, which helps to preserve the ability of the heart to eject blood and reduce adverse events. Therefore, patients with primary PCI should be treated with reperfusion as soon as possible, which is very important to reduce the mortality and adverse clinical events in such patients.

BMI is an important indicator used in the world to assess the degree of obesity and health. There is still debate about the impact of BMI on stent implantation in patients with coronary heart disease. Studies have shown that patients with low body weight have an increased risk of death, while those with overweight and obesity have no significant increase in MACCE and cardiac death.[34] This study showed that BMI >25 kg/m^2 was an independent risk factor for MACCE events. The result is considered to be related to the following factors:

1. All patients in this study were treated with bivalirudin, which reduced the incidence of bleeding events in low-weight patients, thus highlighting the incidence of adverse events in overweight patients.
2. Studies have shown that in patients with coronary heart disease revascularization, metabolic syndrome is an independent predictor of poor prognosis in patients with coronary heart disease compared with traditional risk factors such as hypertension, diabetes, and hyperlipemia.[35]

In this study, there were more patients with metabolic syndrome. Therefore, the increased risk of adverse events caused by BMI may related to this. Combined with the results of this study and previous studies, it is recommended that patients with coronary heart disease should have strict dietary control and ensure appropriate activities when combined with obesity, hypertension, diabetes, hyperlipidemia and other complications, and strengthen monitoring to promote the comprehensive compliance of various targets.

Statins reduce intracellular endogenous cholesterol synthesis and secondary upregulation of cell surface LDL receptors by directly inhibiting the rate-limiting enzyme HMG-CoA activity in cholesterol synthesis, reducing circulating cholesterol levels. A number of studies have demonstrated that statins can reduce the risk of in-stent restenosis and improve the long-term prognosis of patients with acute myocardial infarction.[36] This study also suggests that statins are an independent protective factor for MACCE events in patients after stent implantation. The clinical benefits of statins are not only due to their lowering of cholesterol levels, but also to their multifaceted clinical efficacy, namely the pleiotropic effects of statins. This study also suggests that PPIs are independent protective factors for MACCE. Its protective effect is mainly derived from the protective effect of MACCE secondary to gastrointestinal bleeding. A meta-analysis of 14 clinical trials

found that patients taking 75 to 300 mg of aspirin daily increased the risk of gastrointestinal bleeding by 0.12% per year, and patients with dual antiplatelet drugs had a rate of gastrointestinal bleeding of 1.3% to 2.7%.[37] Therefore, combined PPI drugs can reduce the risk of gastrointestinal bleeding caused by dual antiplatelet therapy. In August 2017, ESC updated the Guideline for Dual Antiplatelet Therapy for coronary artery disease, the combination of PPI and Dual Antiplatelet Therapy recommendation class was upgraded from IIa to Ib. And if you take PPI for more than 1 year, it is recommended to monitor serum magnesium.[38]

5. Conclusions

In summary, in the real world, bivalirudin is safe and effective for coronary intervention, especially in patients with more risk factors for bleeding. However, in female patients and anemia patients, multiple treatments should be taken to prevent the occurrence of bleeding events. When patients with BMI >25 kg/m^2, anemia, KILLIP ≥2, EF value <45%, eGFR <60 ml/minutes, comprehensive treatment should be given to prevent MACCE.

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