


Impact of Diabetes Mellitus on One-Year Clinical Outcomes in Patients Anticoagulated with Bivalirudin Undergoing Elective Percutaneous Coronary Intervention

Clinical and Applied
Thrombosis/Hemostasis
Volume 28: 1-8
© The Author(s) 2022
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/10760296221113344
journals.sagepub.com/home/cat


Yulong Li, MBBS¹, Jiawen Li, MBBS¹, Changdong Guan, MSc¹,
Shuhong Su, MD², Zhifang Wang, MD², Haiwei Liu, MD³,
Bo Xu, MBBS¹, Weixian Yang, MD¹, Yuejin Yang, MD¹,
Runlin Gao, MD¹, Jinqing Yuan, MD¹ , and Xueyan Zhao, MD¹ 

Abstract

Background: Patients with diabetes mellitus (DM) are considered to increase the risk of thrombosis and bleeding. However, whether DM is an independent risk factor for events in patients anticoagulated with bivalirudin during elective percutaneous coronary intervention (PCI) is not clear. **Methods:** Patients anticoagulated with bivalirudin during elective PCI from January 2017 to August 2018 in 3 centers were enrolled. The primary endpoint of thrombotic events was major adverse cardiac and cerebrovascular events (MACCE, including all-cause death, myocardial infarction, ischemic revascularization, stent thrombosis, and stroke); the primary endpoint of bleeding events was Bleeding Academic Research Consortium (BARC) 2, 3 or 5 bleeding. **Results:** 1152 patients were finally enrolled. After one-year follow-up, 89 (7.7%) MACCE and 21 (1.8%) BARC 2, 3 or 5 bleeding occurred. Multivariate Cox regression analysis showed DM was not an independent risk factor for MACCE (hazard ratio [HR]: 1.029, 95% confidence interval [CI]: 0.674-1.573, $P = .893$), but peripheral artery disease (PAD) history (HR: 2.200, 95%CI: 1.290-3.751, $P = .004$) was an independent risk factor for MACCE. DM was not an independent risk factor for BARC 2, 3 or 5 bleeding (HR: 0.732, 95% CI: 0.293-1.831, $P = .505$), but PAD history (HR: 3.029, 95%CI: 1.102-8.332, $P = .032$) and low hemoglobin level (HR = 0.972, 95%CI: 0.947-0.998, $P = .036$) were independent risk factors for BARC 2, 3 or 5 bleeding. **Conclusions:** DM was not an independent risk factor for one-year thrombotic and bleeding events in patients anticoagulated with bivalirudin during elective PCI. More attention should be paid to PAD history and hemoglobin level to identify high-risk patients.

Keywords

diabetes mellitus, elective PCI, bivalirudin, MACCE, bleeding

Date received: 5 April 2022; revised: 8 June 2022; accepted: 27 June 2022.

¹ National Clinical Research Center for Cardiovascular Diseases, State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

² Department of Cardiology, Xinxiang Central Hospital, Xinxiang, China

³ Department of Cardiology, Northern Theatre General Hospital, Shenyang, China

Corresponding Authors:

Xueyan Zhao, National Clinical Research Center for Cardiovascular Diseases, State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, No. 167 Beilishi Road, Xicheng District, Beijing 100037, China.

Email: zhao_xueyan@sina.com

Jinqing Yuan, National Clinical Research Center for Cardiovascular Diseases, State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, No. 167 Beilishi Road, Xicheng District, Beijing 100037, China.

Email: jqyuanfw@163.com



Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons

Attribution-NonCommercial 4.0 License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits non-commercial use,

reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access page (<https://us.sagepub.com/en-us/nam/open-access-at-sage>).

Introduction

Even after percutaneous coronary intervention (PCI), some patients with coronary heart disease (CHD) still have cardiac and cerebrovascular adverse events. Patients with CHD and diabetes mellitus (DM) often have worse clinical outcomes.¹ It is generally believed that patients with CHD and DM not only have a higher risk of thrombotic events, but also an increased risk of bleeding events,² the mechanisms of which may be related to the abnormal glucose metabolism and inflammatory response, including endothelial dysfunction, abnormal pre-thrombotic coagulation, enhanced oxidative stress, and platelet dysfunction.^{3,4} It is important to apply reasonable and effective antithrombotic strategies in patients with CHD complicated with DM.^{5,6}

Bivalirudin is a direct thrombin inhibitor, which is used in anticoagulant therapy during PCI, and compared with unfractionated heparin (UFH), it has the advantages of specificity, reversibility, short half-life, and stronger dose response on thrombin inhibition.⁷ Previously, EUROMAX (The European Ambulance Acute Coronary Syndrome Angiography) trial⁸ showed that compared with UFH, bivalirudin reduced the risk of bleeding events in patients undergoing PCI, but increased the risk of stent thrombosis. Nevertheless, BRIGHT (Bivalirudin in Acute Myocardial Infarction vs Heparin and GPI Plus Heparin Trial)⁹ showed that continuous postoperative infusion of bivalirudin reduced the risk of bleeding without increasing the risk of stent thrombosis and major adverse cardiovascular events (MACE). In patients with DM, Horizons-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) Trial of DM subgroup analysis¹⁰ suggested that DM was not an independent risk factor for bivalirudin in acute myocardial infarction patients undergoing primary PCI. However, whether DM is an independent risk factor for thrombotic and bleeding events in elective PCI patients anticoagulated with bivalirudin has not been reported before.

Therefore, it is urgent to study whether DM affects the occurrence of thrombotic and bleeding events after elective PCI in patients anticoagulated with bivalirudin. This study intends to investigate the impact of DM on one-year thrombotic and bleeding events in patients undergoing elective PCI and anticoagulated with bivalirudin, so as to provide reference for clinical decision-making.

Methods

Study Design and Population

This study was a prospective and multicenter cohort study. Consecutive patients who underwent elective PCI and were anticoagulated with bivalirudin were enrolled from January 2017 to August 2018 in Fuwai Hospital, Northern Theatre General Hospital, and Xinxiang Central Hospital. The inclusion criteria were as follows: patients were aged from 18–85 years old, underwent elective PCI, and were anticoagulated with

bivalirudin in the operation. The exclusion criteria were as follows: acute coronary syndrome (ACS) patients who underwent primary PCI, or patients who took oral anticoagulants with warfarin or non-vitamin K antagonists. Finally, 1152 patients were included in the current analysis. The Declaration of Helsinki protocols were followed. The research protocol was approved by the ethics committee of Fuwai Hospital (Ethics number: 2018-1107). All participants signed informed consents and agreed to follow-up.

Definition and Group Division of DM

DM was defined according to the guidelines on Prevention and Treatment of Diabetes in China. The diagnostic criteria for diabetes were diabetic symptoms with random venous blood glucose levels ≥ 11.1 mmol/L, fasting venous blood glucose levels ≥ 7.0 mmol/L, oral glucose tolerance test 2-h blood glucose levels ≥ 11.1 mmol/L, or use of antidiabetic drugs. According to the diagnosis of DM, patients were divided into DM group ($n = 472$) and non-DM group ($n = 680$).

Study Procedures

Patients were routinely given aspirin and P2Y₁₂ receptor inhibitor (clopidogrel or ticagrelor) preoperatively, while patients who had not previously taken P2Y₁₂ receptor inhibitor were given a loading dose of clopidogrel 300mg or ticagrelor 180 mg one day preoperatively. After PCI, patients were prescribed aspirin 100 mg once daily and clopidogrel 75 mg once daily (or ticagrelor 90 mg twice daily) for at least 1 year. Bivalirudin (Shenzhen Salubris Pharmaceuticals Co., Ltd) was given 0.75 mg/kg through intravenous injection during PCI, followed by 1.75 mg kg⁻¹ h⁻¹ intravenous infusion, and maintained until 3-4 h after PCI. The dose was adjusted according to activated clotting time. Clinical baseline information, procedural characteristics, and outcome data were collected in detail by independent research personnel.

Endpoints and Follow-Up

Primary endpoints included thrombotic endpoint and bleeding endpoint. The thrombotic endpoint was Major Adverse Cardiac and Cerebrovascular Events (MACCE), a composite endpoint consisting of all-cause death, myocardial infarction, stent thrombosis, ischemic revascularization, and stroke. Myocardial infarction was defined according to the third global general definition of myocardial infarction.¹¹ Stent thrombosis was classified as positive, probable or impossible according to the standard definition of Academic Research Consortium.¹² Stroke was diagnosed by a neurologist. The bleeding endpoint was according to the Bleeding Academic Research Consortium (BARC) 2, 3 or 5 bleeding.¹³ Patients were followed-up at one year after discharge by hospital visit or telephone, and the occurrence of MACCE and

bleeding events were recorded in detail. All events were confirmed and recorded by two cardiologists.

Statistical Analysis

Mean with standard deviation was used to describe normally distributed continuous variables, and Student's t-test was used to compare the differences. M (Q₁, Q₃) was used to describe abnormally distributed continuous variables, and Mann-Whitney U test was used to compare the differences. Frequency and percentage were used to describe categorical variables, and Pearson chi-square test and Fisher's exact probability method were used to compare the differences. Kaplan-Meier curve analysis was used to estimate the cumulative survival rates, and log-rank test was used for statistical test. Univariate and multivariate Cox regression analyses were used to explore the influencing factors of MACCE and bleeding events. The Cox proportional hazard model was used to estimate hazard ratios (HRs) and their corresponding confidence intervals (CIs) for the MACCE and BARC 2, 3 or 5 bleeding events. In multivariate Cox regression analysis, MACCE and bleeding events were taken as dependent variables, and DM, gender, age, body mass index (BMI) and factors with statistically significant differences in univariate Cox regression analysis were included as independent variables. All statistical tests were two-sided

with a significant level of 0.05. Statistical analyses were performed with SPSS 25.0 software (IBM Corp., Armonk, New York, USA).

Results

Patients' Characteristics

A total of 1152 patients undergoing elective PCI and anticoagulated with bivalirudin were included in the study. Among them, 472 patients (41.0%) were in the DM group and 680 patients (59.0%) were in the non-DM group. The age of the enrolled patients was (68.6 ± 10.1) years old, including 781 males (67.8%). Among these patients, 178 (15.5%) had ST-elevation myocardial infarction, 115 (10.0%) had non-ST-elevation myocardial infarction, and 859 (74.6%) had angina pectoris. There were 982 patients (85.2%) taking clopidogrel, and 170 patients (14.8%) taking ticagrelor. Compared with the non-DM group, the DM group had more females, higher BMI, more hyperlipidemia and hypertension, less smoking history, more myocardial infarction and PCI history, and lower low-density lipoprotein cholesterol (all *P* < .05) (Table 1).

Clinical Outcomes and Kaplan-Meier Curve Analysis

All patients completed one-year follow-up, and there were 89 (7.7%) MACCE, and 21 (1.8%) BARC 2, 3 or 5 bleeding

Table 1. Baseline Characteristics of Study Population.

Variables	DM group (N = 472)	Non-DM group (N = 680)	P value
Age (years, mean with SD)	68.1 ± 10.1	69.0 ± 10.0	.005
Male (n, %)	298 (63.1%)	483 (71.0%)	.138
BMI (kg/m ² , mean with SD)	27.00 ± 21.54	25.06 ± 3.44	.022
Smoking history (n, %)	249 (52.8%)	401 (59.0%)	.036
COPD history (n, %)	6 (1.3%)	5 (0.7%)	.358
Hyperlipidemia history (n, %)	375 (79.4%)	488 (71.8%)	.003
Hypertension history (n, %)	377 (79.9%)	455 (66.9%)	<.001
Family history of CHD (n, %)	64 (13.6%)	73 (10.7%)	.145
CVD history (n, %)	142 (30.1%)	171 (25.1%)	.064
PAD history (n, %)	55 (11.7%)	58 (8.5%)	.080
MI history (n, %)	148 (31.4%)	177 (26.0%)	.048
PCI history (n, %)	160 (33.9%)	171 (25.1%)	.001
CABG history (n, %)	19 (4.0%)	17 (2.5%)	.143
Use of clopidogrel (n, %)	404 (85.6%)	578 (85.0%)	.780
LVEF [%; M(Q ₁ ,Q ₃)]	61.0 (59.0, 65.0)	62.0 (60.0, 65.0)	.096
WBC [10 ⁹ /L; M(Q ₁ ,Q ₃)]	6.55 (5.50, 7.71)	6.49 (5.40, 7.65)	.323
HB [g/L; M(Q ₁ ,Q ₃)]	142.00 (132.00, 152.00)	144.00 (130.25, 154.00)	.103
PLT [10 ⁹ /L; M(Q ₁ ,Q ₃)]	216.50 (183.00, 263.75)	221.00 (184.00, 268.75)	.239
LDL-C [mmol/L; M(Q ₁ ,Q ₃)]	2.29 (1.73, 2.62)	2.36 (1.90, 2.75)	.017
hs-CRP [mmol/L; M(Q ₁ ,Q ₃)]	1.90 (0.83, 3.13)	2.21 (0.96, 3.22)	.277
Number of stents (n, mean with SD)	1.65 ± 1.03	1.64 ± 0.98	.858
Femoral approach (n, %)	46 (9.7%)	62 (9.1%)	.719
IABP (n, %)	7 (1.5%)	6 (0.9%)	.343

Abbreviations: DM, diabetes mellitus; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CHD, coronary heart disease; CVD, cerebrovascular disease; PAD, peripheral artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; LVEF, left ventricular ejection fraction; WBC, white blood count; HB, hemoglobin; PLT, platelet; LDL-C, low density lipoprotein cholesterol; hs-CRP, high sensitive - C reactive protein; IABP, intra-aortic balloon pump.

events occurred. MACCE (8.1% vs 7.5%, $P=.731$) and its components (including all-cause death, myocardial infarction, ischemic revascularization, stent thrombosis, and stroke), and BARC 2, 3 or 5 bleeding (1.5% vs 2.1%, $P=.473$) had no statistically significant difference between DM-group and non-DM group (all $P>.05$) (Table 2). Kaplan-Meier curve analysis showed there was no significant difference in the cumulative incidence of MACCE and BARC 2, 3 or 5 bleeding (log-rank test, all $P>.05$) (Figure 1).

Univariate Cox Regression Analysis

Univariate Cox regression analysis showed DM had no effect on the occurrence of one-year MACCE in patients anticoagulated with bivalirudin during elective PCI (HR: 1.081, 95% CI: 0.711-1.646, $P=.715$), while peripheral artery disease (PAD) history (HR: 2.238, 95%CI: 1.319-3.796, $P=.003$) and white blood cell counts (HR: 1.110, 95%CI: 1.004-1.227, $P=.042$) were associated with MACCE; DM had no effect on the occurrence of one-year BARC 2, 3 or 5 bleeding (HR: 0.718, 95%CI: 0.290-1.779, $P=.474$), while age (HR: 1.070, 95%CI: 1.011-1.131, $P=.018$), PAD history (HR: 2.913, 95%CI: 1.067-7.952, $P=.037$), and hemoglobin level (HR: 0.970, 95%CI: 0.948-0.993, $P=.010$) were associated with BARC 2, 3 or 5 bleeding. (Table 3)

Multivariate Cox Regression Analysis

After adjusting for age, gender, BMI, and factors with statistically significant differences in univariate Cox regression analysis, multivariate Cox regression analysis showed that DM was not an independent risk factor for one-year MACCE in patients anticoagulated with bivalirudin during elective PCI (HR: 1.029, 95%CI: 0.674-1.573, $P=.893$), while PAD history (HR: 2.200, 95%CI: 1.290-3.751, $P=.004$) was an independent risk factor for MACCE; DM was not an independent risk factor for BARC 2, 3 or 5 bleeding (HR: 0.732, 95%CI: 0.293-1.831, $P=.505$), while PAD history (HR: 3.029, 95%CI: 1.102-8.332, $P=.032$) and low hemoglobin level (HR: 0.972, 95%CI: 0.947-0.998, $P=.036$) were independent risk factors for BARC 2, 3 or 5 bleeding. (Table 4)

Table 2. Clinical Outcomes Between DM and Non-DM Group.

Endpoints	DM group (N = 472)	Non-DM group (N = 680)	P value
MACCE	38 (8.1%)	51 (7.5%)	.731
Death	2 (0.4%)	12 (1.8%)	.077
Myocardial infarction	2 (0.4%)	0 (0.0%)	.168
Revascularization	31 (6.6%)	34 (5.0%)	.257
Intrastent thrombosis	2 (0.4%)	1 (0.1%)	.750
Stroke	6 (1.3%)	7 (1.0%)	.702
BARC 2, 3 or 5 bleeding	7 (1.5%)	14 (2.1%)	.473

Abbreviations: MACCE, major adverse cardiac and cerebrovascular events; BARC, bleeding academic research consortium.

Discussion

This study is the first to investigate whether DM affects the occurrence of one-year MACCE and bleeding events in patients undergoing elective PCI and anticoagulated with bivalirudin. The results showed as follows: DM did not affect the occurrence of one-year MACCE in patients anticoagulated with bivalirudin during elective PCI, while PAD history was an independent risk factor for MACCE; DM did not affect the occurrence of one-year BARC 2, 3 or 5 bleeding in patients anticoagulated with bivalirudin during elective PCI, while PAD history and low hemoglobin level were independent risk factors for BARC 2, 3 or 5 bleeding.

In this study, DM did not affect the occurrence of one-year MACCE in patients anticoagulated with bivalirudin during elective PCI. At present, the conclusions about whether DM can affect the thrombotic events in patients undergoing PCI are not uniform. For patients anticoagulated with heparin during PCI, EPICOR Asia Study (long-term follow-up of Antithrombotic Management Patterns in Acute Coronary Syndrome Patients in Asia Study)¹⁴ indicated that, DM significantly increased the risk of two-year thrombotic events after PCI in ACS patients. However, Wang HH et al¹⁵ did not find that DM was an independent predictor of two-year MACE after PCI in a cohort study of 10 724 patients undergoing PCI, including patients with ACS and chronic coronary syndrome. In a five-year long-term follow-up study, Zibaenezhad et al¹⁶ also concluded that DM could not be an independent predictor of MACE after PCI. The above results are inconsistent, which may be related to whether the ACS population are included, and additionally, the patients' year of inclusion. It should be noted that heparin was used for anticoagulation in all the studies above. We reported for the first time that, in patients anticoagulated with bivalirudin during elective PCI, DM was not a risk factor for one-year MACCE. However, our study enrolled patients from January 2017 to August 2018, which is not relatively new. In recent years, the new drug therapies and drug-eluting stents are developing rapidly in CHD area. New hypoglycemic drugs, such as sodium-glucose cotransporter protein-2 inhibitors and glucagon-like peptide-1 receptor agonists, were reported to lower death, non-fatal myocardial infarction and other cardiovascular outcomes in DM patients.¹⁷ As a result, further investigation could be carried out to test their effect in DM patients undergoing elective PCI and anticoagulated with bivalirudin.

In addition, our study also found that PAD history was an independent risk factor for one-year MACCE in patients anticoagulated with bivalirudin during elective PCI. In patients with stable CHD, Cheng et al¹⁸ suggested that PAD was an independent risk factor for cardiovascular events after PCI. Franzone et al¹⁹ showed that among patients with stable CHD and ACS who received PCI, patients with PAD had poor prognosis. Our findings are consistent with the above studies, suggesting that PAD history is an independent risk factor for thrombotic events after PCI regardless of using bivalirudin or heparin. The current guidelines also recommend focusing on revascularization

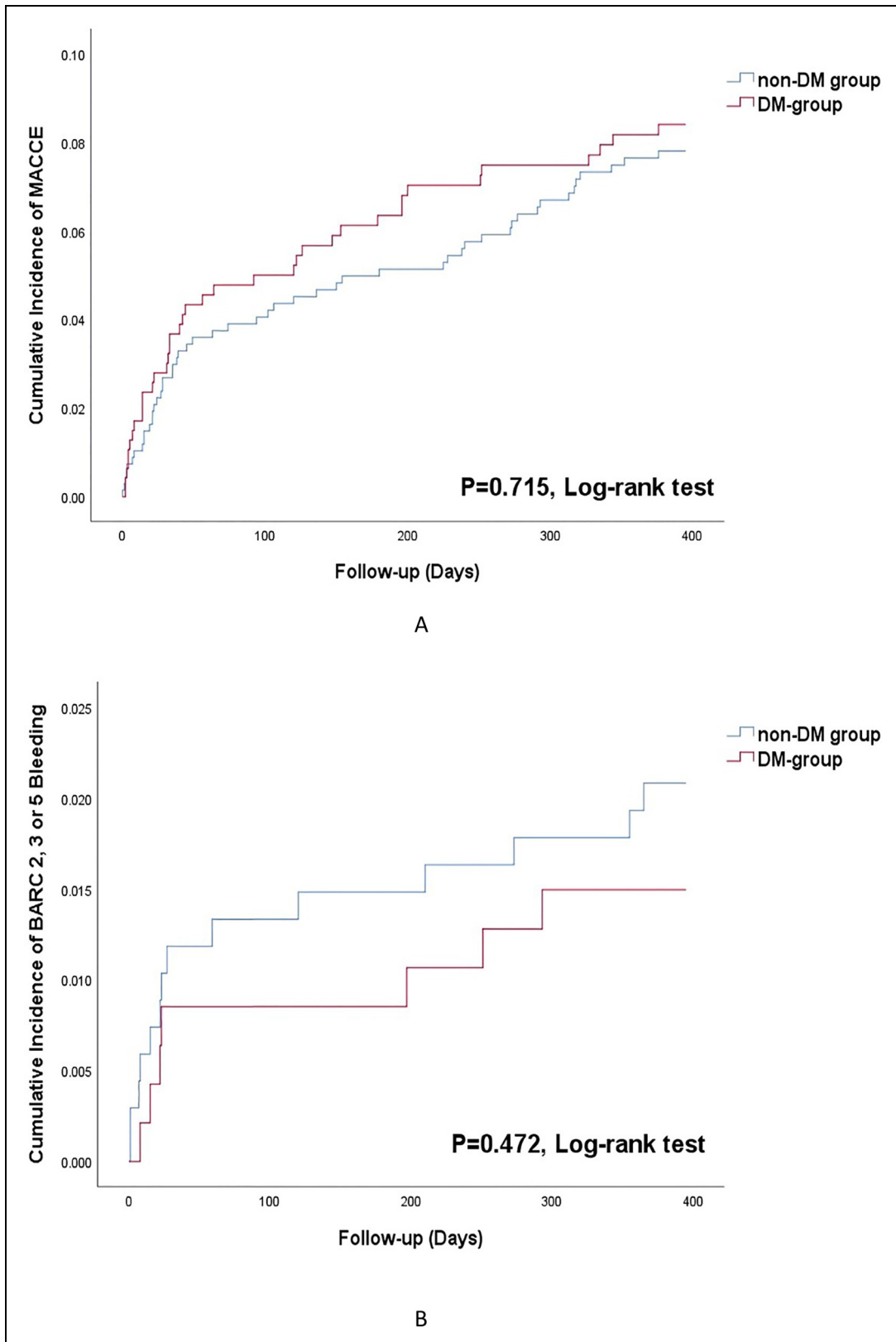


Figure 1. Kaplan-Meier curve analysis of MACCE (A) and BARC 2, 3 or 5 bleeding (B).
Note: No significant difference was found in the cumulative incidence of MACCE ($P = .715$, log-rank test) and BARC 2, 3 or 5 bleeding ($P = .472$, log-rank test).
Abbreviations: MACCE, Major Adverse Cardiac and Cerebrovascular Events; BARC, Bleeding Academic Research Consortium.

Table 3. Univariate Cox Regression Analysis of MACCE and BARC 2, 3 or 5 Bleeding.

Variables	MACCE			BARC 2, 3 or 5 bleeding		
	HR	95% CI	P value	HR	95% CI	P value
DM	1.081	0.711-1.646	.715	0.718	0.290-1.779	.474
Age	0.987	0.968-1.007	.201	1.070	1.011-1.131	.018
Male	1.149	0.727-1.814	.552	0.767	0.318-1.850	.555
BMI	0.999	0.983-1.061	.930	0.942	0.828-1.073	.369
Smoking history	1.081	0.709-1.649	.716	1.257	0.521-3.032	.611
COPD history	1.142	0.159-8.194	.895	0.049	0-1.579*10 ⁷	.763
Hyperlipidemia history	0.852	0.537-1.353	.498	1.071	0.392-2.922	.849
Hypertension history	0.930	0.589-1.468	.755	0.768	0.310-1.904	.569
Family history of CHD	1.051	0.559-1.975	.878	1.236	0.364-4.195	.734
CVD history	1.240	0.793-1.939	.346	0.443	0.131-1.504	.192
PAD history	2.238	1.319-3.796	.003	2.913	1.067-7.952	.037
MI history	1.102	0.701-1.732	.674	1.930	0.813-4.579	.136
PCI history	1.061	0.643-1.604	.946	1.244	0.502-3.083	.637
CABG history	1.498	0.549-4.083	.430	1.577	0.212-11.753	.656
Clopidogrel use	1.387	0.718-2.678	.330	1.661	0.387-7.129	.495
LVEF	0.982	0.995-1.009	.181	1.014	0.948-1.085	.679
WBC	1.110	1.004-1.227	.042	0.980	0.777-1.237	.868
HB	1.004	0.992-1.017	.507	0.970	0.948-0.993	.010
PLT	1.001	0.998-1.004	.343	0.997	0.990-1.004	.357
LDL-C	0.876	0.666-1.151	.324	0.564	0.291-1.091	.089
hs-CRP	1.030	0.970-1.092	.334	0.993	0.869-1.135	.920

Abbreviations: MACCE, major adverse cardiac and cerebrovascular events; BARC, bleeding academic research consortium; HR, hazard ratio; CI, confidence interval; DM, diabetes mellitus; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CHD, coronary heart disease; CVD, cerebrovascular disease; PAD, peripheral artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; LVEF, left ventricular ejection fraction; WBC, white blood count; HB, hemoglobin; PLT, platelet; LDL-C, low density lipoprotein cholesterol; hs-CRP, high sensitive – C reactive protein.

Table 4. Multivariate Cox Regression Analysis of MACCE and BARC 2, 3 or 5 Bleeding.

Variables	MACCE			BARC 2, 3 or 5 bleeding		
	HR	95% CI	P value	HR	95% CI	P value
DM	1.029	0.674-1.573	.893	0.732	0.293-1.831	.505
Age	0.987	0.967-1.008	.225	1.055	0.996-1.118	.068
Male	1.016	0.633-1.630	.947	1.230	0.478-3.165	.668
BMI	0.998	0.978-1.019	.872	0.994	0.920-1.075	.888
PAD history	2.200	1.290-3.751	.004	3.029	1.102-8.332	.032
WBC	1.095	0.990-1.211	.079	—	—	—
HB	—	—	—	0.972	0.947-0.998	.036

Abbreviations: MACCE, major adverse cardiac and cerebrovascular events; BARC, bleeding academic research consortium; HR, hazard ratio; CI, confidence interval; DM, diabetes mellitus; BMI, body mass index; PAD, peripheral artery disease; WBC, white blood count; HB, hemoglobin.

strategies for CHD patients with PAD, so as to reduce the occurrence of adverse clinical outcomes in such patients.⁵

Our study also indicated that DM did not affect the occurrence of one-year BARC 2, 3 or 5 bleeding in patients anticoagulated with bivalirudin during elective PCI. At present, the conclusions about whether DM can affect the bleeding events in patients undergoing PCI are also controversial. Recently, Luca et al²⁰ showed that DM did not increase the risk of one-year ischemic events after PCI in elderly patients anticoagulated with heparin, but significantly increased the risk of one-year bleeding events after PCI. Similarly, Jarrah et al's study² on PCI population showed that DM significantly

increased the risk of bleeding after PCI. However, Guan S et al's study¹⁴ on the ACS population and Pembele et al's study²¹ both showed that diabetes was not an independent influencing factor of bleeding events after PCI. Notably, heparin was used in all of the studies above, while bivalirudin was used in our study. Our study showed that DM was not a risk factor for increased bleeding events in patients anticoagulated with bivalirudin during elective PCI. The reason for this result may be related to the attention paid to patients with high bleeding risk in recent years, so that clinicians have taken effective management of relevant patients. More patients with high bleeding risk have used proton pump inhibitors, and the majority of

patients choose the radial artery approach in PCI procedure. Evidence supported that the above measures could reduce the risk of bleeding after PCI,^{22,23} and the application of bivalirudin in DM patients also reduced the risk of bleeding events compared with heparin.²⁴

Additionally, our study also found that PAD history and low hemoglobin level were independent risk factors for one-year BARC 2, 3 or 5 bleeding in patients anticoagulated with bivalirudin during elective PCI. Previous studies using heparin for anticoagulation also supported the independent correlation between PVD and hemoglobin and bleeding events after PCI. PAD history is an important component of the CREDO-Kyoto bleeding prediction model,²⁵ and it is also an important indicator of the CRUSADE bleeding score.²⁶ Low baseline hemoglobin level is an important risk factor in PARIS score²⁷ and PRECISE-DAPT score.²⁸ Kalra et al²⁹ suggested that low baseline hemoglobin level was associated with an increased risk of bleeding after PCI for stable CHD patients. Faggioni et al³⁰ demonstrated that low baseline hemoglobin level was an independent risk factor for bleeding after PCI in ACS patients. These conclusions are consistent with the results of our study, in which patients were anticoagulated with bivalirudin. The current guidelines also recommend focusing on CHD patients with anemia to reduce the incidence of bleeding outcomes in these patients.⁶

In summary, the impact of diabetes on patients anticoagulated with heparin during PCI remains controversial. We conducted an exploratory study in the real world of patients undergoing elective PCI and anticoagulated with bivalirudin, and the results showed that DM was not a risk factor for one-year MACCE and bleeding events, which indicates that the use of bivalirudin is not affected by DM. In addition, our study suggests that in elective PCI patients anticoagulated with bivalirudin, more attention should be paid to PAD history and hemoglobin level to identify patients with potential high risk of thrombotic and bleeding events, and individualized treatment may reduce the occurrence of adverse clinical outcomes.

Limitations

There are some limitations in our study. First, this study is an observational study, and randomized controlled trial with a larger sample size could be carried out in the future to evaluate the impact of DM on clinical outcomes in patients anticoagulated with bivalirudin during elective PCI. Second, this study enrolled patients from January 2017 to August 2018, which is not relatively new and did not evaluate the effect of new drug therapy on diabetes. Third, the lack of duration of DM may be a limitation of this study.

Conclusions

In patients undergoing elective PCI and anticoagulated with bivalirudin, DM was not an independent risk factor for one-year thrombotic and bleeding events. More attention should be paid to PAD history and hemoglobin level to identify

patients with potential high risk of thrombotic and bleeding events.

Abbreviations

PCI	percutaneous coronary intervention
CHD	coronary heart disease
DM	diabetes mellitus
UFH	unfractionated heparin
MACE	major adverse cardiovascular events
ACS	acute coronary syndrome
MACCE	major adverse cardiac and cerebrovascular events
BARC	bleeding academic research consortium
HR	hazard ratio
CI	confidence interval
BMI	body mass index
PAD	peripheral artery disease.

Acknowledgements

The authors are grateful to the individuals who participated in this study, and grateful to all the funding supported us: the CS Optimizing Antithrombotic Research Fund (CRFH20180082), Young and middle-aged talents in the XPCC Science and Technology Project (2020CB012), CAMS Innovation Fund for Medical Sciences (CIFMS) (2020-I2M-C&T-B-052) and the National Key Research and Development Program of China (No. 2016YFC1301300 and No. 2016YFC1301301).

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the the National Key Research and Development Program of China, Young and middle-aged talents in the XPCC Science and Technology Project, the CS Optimizing Antithrombotic Research Fund, CAMS Innovation Fund for Medical Sciences (CIFMS), (grant number No. 2016YFC1301300 and No. 2016YFC1301301, 2020CB012, CRFH20180082, 2020-I2M-C&T-B-052).

Ethics Approval and Consent to Participate

Ethical approval to report this study was obtained from the local ethics committee of the Fuwai hospital's Research Ethics Committee (Ethics number: 2018-1107). Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

ORCID iDs

Jinqing Yuan  <https://orcid.org/0000-0001-7259-511X>
Xueyan Zhao  <https://orcid.org/0000-0002-8024-7024>

References

1. Damaskos C, Garmpis N, Kollia P, et al. Assessing cardiovascular risk in patients with diabetes: an update. *Curr Cardiol Rev.* 2020;16(4):266–274.

2. Jarrah MI, Al-Khatib S, Khader Y, et al. The impact of coexistence of smoking and diabetes on the coronary artery severity and outcomes following percutaneous coronary intervention: results from the 1(ST) Jordanian PCI registry. *Int J Vasc Med.* 2020;2020:7624158. doi: 10.1155/2020/7624158.
3. Vazzana N, Ranalli P, Cucurullo C, Davi G. Diabetes mellitus and thrombosis. *Thromb Res.* 2012;129(3):371–377.
4. Babik B, Peták F, Agócs S, et al. Diabetes mellitus: endothelial dysfunction and changes in hemostasis. *Orv Hetil.* 2018;159(33):1335–1345.
5. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J.* 2019;40(2):87–165.
6. Collet JP, Thiele H, Barbato E, et al. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J.* 2021;42(14):1289–1367.
7. Shammas NW. Bivalirudin: pharmacology and clinical applications. *Cardiovasc Drug Rev.* 2005;23(4):345–360.
8. Steg PG, van't Hof A, Hamm CW, et al. Bivalirudin started during emergency transport for primary PCI. *N Engl J Med.* 2013;369(23):2207–2217.
9. Han Y, Guo J, Zheng Y, 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(13):1336–1346.
10. Witzenbichler B, Mehran R, Guagliumi G, et al. Impact of diabetes mellitus on the safety and effectiveness of bivalirudin in patients with acute myocardial infarction undergoing primary angioplasty: analysis from the HORIZONS-AMI (harmonizing outcomes with RevascularizatiON and stents in acute myocardial infarction) trial. *JACC Cardiovasc Interv.* 2011;4(7):760–768.
11. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *J Am Coll Cardiol.* 2012;60(16):1581–1598.
12. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation.* 2007;115(17):2344–2351.
13. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation.* 2011;123(23):2736–2747.
14. Guan S, Xu X, Li Y, et al. Impact of diabetes mellitus on antithrombotic management patterns and long-term clinical outcomes in patients with acute coronary syndrome: insights from the EPICOR Asia study. *J Am Heart Assoc.* 2020;9(22):e013476.
15. Wang H, Gao Z, Song Y, et al. Impact of diabetes mellitus on percutaneous coronary intervention in Chinese patients: a large single-center data. *Angiology.* 2018;69(6):540–547.
16. Zibaenezhad MJ, Mohammadi SS, Sayadi M, Khorshidi S, Bahramali E, Razeghian-Jahromi I. The impact of diabetes mellitus and hypertension on clinical outcomes in a population of Iranian patients who underwent percutaneous coronary intervention: a retrospective cohort study. *J Clin Hypertens.* 2019;21(11):1647–1653.
17. Palmer SC, Tendal B, Mustafa RA, et al. Sodium-glucose cotransporter protein-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists for type 2 diabetes: systematic review and network meta-analysis of randomised controlled trials. *Br Med J.* 2021;372:m4573. doi: 10.1136/bmj.m4573.
18. Cheng Z, Qi M, Lang Z, et al. Peripheral artery disease on the prognosis value of patients with stable coronary artery disease undergoing percutaneous coronary intervention: a retrospective, single-center cohort study. *Heart Surg Forum.* 2021;24(5):E887–e892.
19. Franzone A, Piccolo R, Gargiulo G, et al. Prolonged vs short duration of dual antiplatelet therapy after percutaneous coronary intervention in patients with or without peripheral arterial disease: a subgroup analysis of the PRODIGY randomized clinical trial. *JAMA Cardiol.* 2016;1(7):795–803.
20. De Luca G, Verdoia M, Savonitto S, et al. Impact of diabetes on clinical outcome among elderly patients with acute coronary syndrome treated with percutaneous coronary intervention: insights from the ELDERLY ACS 2 trial. *J Cardiovasc Med.* 2020;21:453–459. doi: 10.2459/jcm.0000000000000978.
21. M'Pembale R, Metzen D, Czychy N, et al. Diabetes mellitus is not associated with enhanced bleeding risk in patients after percutaneous coronary intervention. *Diabet Med.* 2021;38(5):e14532.
22. Bhatt DL, Cryer BL, Contant CF, et al. Clopidogrel with or without omeprazole in coronary artery disease. *N Engl J Med.* 2010;363(20):1909–1917.
23. Karrowni W, Vyas A, Giacomino B, et al. Radial versus femoral access for primary percutaneous interventions in ST-segment elevation myocardial infarction patients: a meta-analysis of randomized controlled trials. *JACC Cardiovasc Interv.* 2013;6(8):814–823.
24. Zhang J, Yang X. Efficacy and safety of bivalirudin versus heparin in patients with diabetes mellitus undergoing percutaneous coronary intervention: a meta-analysis of randomized controlled trials. *Medicine (Baltimore).* 2017;96(29):e7204.
25. Natsuaki M, Morimoto T, Yamaji K, et al. Prediction of thrombotic and bleeding events after percutaneous coronary intervention: CREDO-Kyoto thrombotic and bleeding risk scores. *J Am Heart Assoc.* 2018;7(11). doi: 10.1161/jaha.118.008708.
26. Subherwal S, Bach RG, Chen AY, et al. Baseline risk of major bleeding in non-ST-segment-elevation myocardial infarction: the CRUSADE (can rapid risk stratification of unstable angina patients suppress ADverse outcomes with early implementation of the ACC/AHA guidelines) bleeding score. *Circulation.* 2009;119(14):1873–1882.
27. Baber U, Mehran R, Giustino G, et al. Coronary thrombosis and major bleeding after PCI with drug-eluting stents: risk scores from PARIS. *J Am Coll Cardiol.* 2016;67(19):2224–2234.
28. Costa F, van Klaveren D, James S, et al. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. *Lancet.* 2017;389(10073):1025–1034.
29. Kalra PR, Greenlaw N, Ferrari R, et al. Hemoglobin and change in hemoglobin status predict mortality, cardiovascular events, and bleeding in stable coronary artery disease. *Am J Med.* 2017;130(6):720–730.
30. Faggioni M, Baber U, Sartori S, et al. Influence of baseline anemia on dual antiplatelet therapy cessation and risk of adverse events after percutaneous coronary intervention. *Circ Cardiovasc Interv.* 2019;12(4):e007133.