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On-label vs. off-label use of vascular closure devices in Japanese patients undergoing percutaneous coronary intervention

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KEYWORDS

- percutaneous coronary intervention
- vascular closure device

Abstract

Aims: Vascular closure devices (VCD) provide immediate haemostasis and enable early mobilisation for patients undergoing percutaneous coronary intervention (PCI). At present, the use of VCD in Japan is only approved for elective PCI patients who are expected to be discharged within 48 hrs. The aim of this study was to clarify the safety of VCD use in on- and off-label cases.

Methods and results: We analysed 7,901 consecutive patients undergoing a femoral-approach PCI between 2008 and 2014 at 13 hospitals in Japan. We compared in-hospital outcomes of VCD users to VCD non-users (control). In addition, propensity score matching analyses were performed for on- and off-label VCD users, subsequently generating two matched data sets consisting of 2,626 patients (with on-label), and 626 patients (with off-label), respectively. The patients' average age was 67.7±11.1 and 54.5% presented with ACS. Overall, 20.8% used VCD for haemostasis, and the crude in-hospital vascular complication rates were not different between the VCD users and the controls (2.0% vs. 2.1%, p=0.741). Female gender was the only variable associated with a risk of vascular complication among VCD users (OR 3.12, 95% CI: 1.45-6.71, p=0.004). Even after propensity score matching, the incidence of vascular complications did not differ among VCD users and the control group for either the on-label (2.0 vs. 2.1%, p=0.783) or off-label data set (2.2 vs. 1.6%, p=0.560).

Conclusions: VCD users had a similar bleeding complication rate to the controls, including in patients with off-label use. Further studies are necessary to confirm the safety of VCD in different scenarios.

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Abbreviations

AHA	American Heart Association
BMI	body mass index
CPA	cardiopulmonary arrest
CS	cardiogenic shock
DES	drug-eluting stent
IABP	intra-aortic balloon pump
JCD-KiCS	Japanese Cardiovascular Database-Keio interhospital Cardiovascular Studies
PCI	percutaneous coronary intervention
STEMI	ST-elevation myocardial infarction
VCD	vascular closure device(s)

Introduction

Periprocedural bleeding is the most common complication of percutaneous coronary intervention (PCI) and is associated with a risk of early mortality[1-4]. Vascular closure devices (VCD) provide immediate haemostasis and enable early mobilisation for patients undergoing PCI. However, data of bleeding risk with VCD have revealed mixed results; the use of VCD seemed to increase the vascular complication rate in a subset of patients with increased body habitus, complex arterial anatomy, small-sized and non-patent vessel, larger sheath size and systemic disease[5,6]. Further, VCD for emergent cases could potentially lead to an increased rate of bleeding complications when compared with elective PCI[7]. The most recent American Heart Association (AHA) statement provides a class IIa recommendation for faster haemostasis and a shorter duration of bed rest, and a class III recommendation for the routine use of VCD to reduce vascular complications.

In Japan, VCD are approved for use in patients who are expected to be discharged within 48 hrs after the PCI procedure. This application of the device is intended for early mobilisation and, consequently, early discharge. Asian patients are known to have higher rates of bleeding complications compared with patients in Western countries[8], and such concerns and cost issues have led to the limited use of VCD. However, at times, VCD are used off-label[9], such as in cases of ST-elevation myocardial infarction (STEMI).

To date, there has not been any clinical validation of the use of VCD in real-world situations[9]. Hence, the aim of this study was to investigate whether VCD are safe for Japanese patients who undergo PCI, irrespective of VCD indication.

Methods

The Japanese Cardiovascular Database-Keio interhospital Cardiovascular Studies (JCD-KiCS) is a large, ongoing, prospective, multicentre cohort study designed to collect clinical background and outcome data on PCI patients. Participating hospitals were instructed to record data from hospital visits for consecutive PCI patients and to register these data in an internet-based database. Data pertaining to approximately 150 variables are being collected. There are dedicated clinical research coordinators assigned to each site, and a web-based system performs checks to ensure that the reported data are complete and internally consistent. PCI performed using any coronary device may be included. The decision to perform PCI is made based on the attending physician's clinical assessments. The study does not mandate specific interventional or surgical techniques, such as vascular access, sheath size or use of a specific stent or VCD.

Although the sizes of the sheath and guiding catheter were not protocol-mandated in this cohort, the commonly used size was 6-8 Fr in a transfemoral intervention. Since GP IIb/IIIa inhibitors and bivalirudin are not available in Japan, all patients underwent periprocedural anticoagulation via heparin based on institutional dosing instructions during PCI. Usually a bolus dose of 5,000-10,000 IU was given, with additional doses provided based on an activated clotting time of >300 s during PCI[10]. The recommended antiplatelet therapy was long-term aspirin 81 mg daily, along with a thienopyridine (75 mg clopidogrel or 200 mg ticlopidine daily). In general, the loading dose of clopidogrel was 300 mg. Prasugrel was available from March 2014, but ticagrelor was not available in Japan.

Major teaching hospitals within the Tokyo metropolitan area were selected for the study, and the study protocol was approved by an institutional review board committee at each site. In this registry, the data have been collected since September 2008 from 12 Japanese hospitals participating in the JCD[11-16]. Prior to the launch of the JCD, information on the study objectives, social significance, and an abstract were provided to register this clinical trial with the University Hospital Medical Information Network. This network is recognised by the International Committee of Medical Journal Editors as an acceptable registry, according to a statement issued in September 2004 (UMIN R000005598).

Data were analysed from the 7,901 patients who underwent consecutive PCI with a transfemoral approach between September 2008 and March 2014 **(Figure 1)**. We divided all patients into two groups according to the kind of VCD use (on-label indication group and off-label indication group). The on-label use of VCD was defined as the use of VCD for non-urgent/elective patients and those anticipated to be discharged within 48 hrs after PCI. Any use of VCD for critically ill patients (who clearly need to stay at the hospital for >48 hrs after PCI) would be considered off-label (e.g., in those patients with ST-elevation myocardial infarction [STEMI][17], cardiogenic shock [CS], cardiopulmonary arrest [CPA], or use of an intra-aortic balloon pump [IABP]). Thus, we defined the off-label indication group as those with STEMI, CS, CPA, and IABP, while the on-label indication group included the others.

We analysed baseline characteristics and clinical outcomes, and compared VCD use (VCD users) with manual compression (control) in each group. Currently in Japan, Angio-Seal™ (St. Jude Medical, St. Paul, MN, USA), Perclose (Abbott Vascular, Santa Clara, CA, USA) and ExoSeal® (Cordis, Johnson & Johnson, New Brunswick, NJ, USA) are available as VCD for on-label PCI use, albeit ExoSeal was not used in our study since it was introduced into the market very recently.

The majority of the clinical variables in the JCD were defined according to the National Cardiovascular Data Registry, sponsored

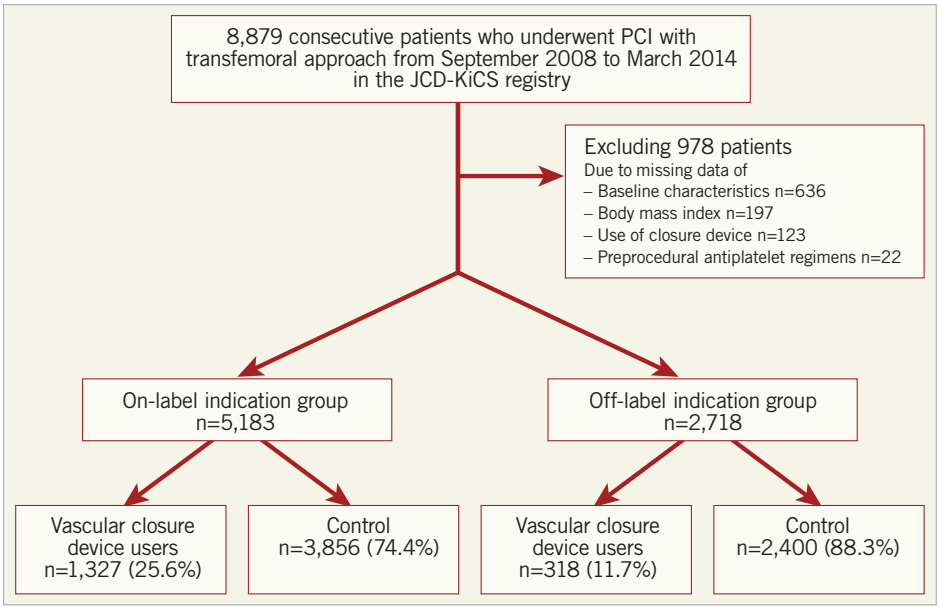

Figure 1. *Patient flow chart.*

by the American College of Cardiology, to conduct comparative research and determine the factors that lead to disparities in PCI management[18,19].

The study endpoints were vascular complications and other complications. Vascular complication was defined as the composite of puncture-site bleeding, puncture-site haematoma, and peritoneal bleeding. Puncture-site bleeding consisted of significant external bleeding that occurred at the access or percutaneous entry site and was associated with any of the following: haemoglobin drop of >3.0 g/dl[20], requiring transfusion, procedural intervention/surgery at the bleeding site to reverse/stop or correct the bleeding, and acute anaemia with a reduction in haemoglobin of >3.0 g/dl without other obvious sources or intraprocedural blood loss. Puncture-site haematoma was defined as haematoma >10 cm. These definitions were in accordance with the National Cardiovascular Data Registry (http://www.ncdr.com/webncdr/cathpci/). Bleeding criteria are also consistent with the Bleeding Academic Research Consortium grades 3A to C[21]. Other complications included in-hospital mortality, heart failure, cardiogenic shock, severe dissection or coronary perforation, myocardial infarction after PCI, cardiogenic shock or heart failure, cerebral bleeding or stroke, gastrointestinal bleeding, genitourinary bleeding, or other bleeding.

STATISTICAL ANALYSIS

Continuous variables are expressed as means and standard deviations, or median (interquartile range), and categorical variables are expressed as percentages. Continuous variables were compared using a Student's t-test or Mann-Whitney U test, and differences between categorical variables were examined using a χ^2 test or Fisher's exact test. A multivariate logistic regression analysis was performed to determine the independent predictors for vascular complications among patients who received VCD. A univariate logistic regression analysis was performed, and factors with a p-value <0.25 and off-label use were included in the multivariate analysis.

For the propensity score matching analysis, the model covariates consisted of sex, body mass index (BMI) <18.5[22], previous myocardial infarction, previous heart failure, diabetes mellitus, dialysis, cerebrovascular disease, peripheral artery disease, chronic lung disease, smoking, hypertension, dyslipidaemia, previous PCI, previous coronary bypass, congestive heart failure at admission, age >80, preprocedural aspirin and clopidogrel for both groups, and STEMI, CS at admission, CPA at admission, IABP insertion for the off-label group, and unstable angina/non-ST-elevation myocardial infarction for the on-label group. A propensity score was developed using a logistic regression conditioned on these covariates. A 1:1 match was performed using a nearest neighbour match within a calliper of 1/5 of the standard deviation of the logit of the propensity model[23]. All statistical calculations and analyses were performed using SPSS, Version 22 (IBM Corp., Armonk, NY, USA), and p-values <0.05 were considered statistically significant.

Results

Among all 7,901 patients, the average age was 67.7±11.1 and 4,308 patients (54.5%) presented with acute coronary syndrome. A total of 1,645 patients (20.8%) received VCD and 1,464 (18.5%) patients received the Angio-Seal (89.0% of patients with the use of VCD). Crude vascular complication rates were not significantly different with different uses of VCD (VCD users vs. control; 2.0% vs. 2.1%, p=0.741). Among all patients who received VCD (n=1,645), patients on off-label use (n=318) were leaner (BMI: 23.8±3.8 vs. 24.5±3.5, p=0.007), and had a higher proportion of

age >80 (17.3% vs. 12.1%, p=0.015) compared with on-label use (n=1,328) **(Table 1)**. The average ages were not significantly different in either group (off-label use vs. on-label use: 66.5±12.7 vs. 67.8±10.6, p=0.106). In-hospital clinical outcomes are shown in **Table 2**. Vascular complications were not significantly different in each group (off-label use vs. on-label use: 2.2% vs. 2.0%, p=0.782). When a logistic regression modelling was performed, after adjustment, female gender was the only variable that was associated with vascular complications in patients in whom a VCD was used (odds ratio [OR] 3.12, confidence interval [CI]: 1.45-6.71, p=0.004). Notably, the off-label use of VCD, along with variables such as lower BMI or age >80, was not associated with an increased risk of vascular complications **(Table 3)**.

Overall, 2,718 (34.4%) patients out of 7,901 presented with STEMI, CS, CPA, and use of IABP, which were thought to be off-label indications with respect to the use of VCD **(Figure 1)**. In the on-label indication group (n=5,183), 1,327 (25.6%) patients received VCD. Baseline characteristics and in-hospital outcomes are shown in **Table 4** and **Table 5**. Vascular complications were not significantly different regardless of the use of VCD (VCD users vs. control: 2.0% vs. 1.9%, p=0.974). In the off-label indication group (n=2,718), 318 (11.7%) patients received VCD. Baseline characteristics and in-hospital outcomes for these patients are shown in **Table 6** and **Table 7**. Vascular complications were not significantly different regardless of the use of VCD (VCD vs. control: 2.2% vs. 2.4%, p=0.848).

Since baseline characteristics were significantly different in VCD users and controls in the on- and off-label indication groups, we performed a propensity score matching analysis in each group

Table 1. Baseline characteristics in vascular closure device users.

		Off-label users n=318 (%)	On-label users n=1,327 (%)	*p*-value
Age (years)		66.5±12.7	67.8±10.6	0.106
Age >80		55 (17.3%)	161 (12.1%)	0.014
Female		74 (23.3%)	275 (20.7%)	0.318
Body mass index		23.8±3.8	24.5±3.5	0.007
Body mass index <18.5		20 (6.3%)	47 (3.5%)	0.026
Previous myocardial infarction		40 (12.6%)	370 (27.9%)	<0.001
Previous heart failure		15 (4.7%)	126 (9.5%)	0.006
Diabetes mellitus		112 (35.2%)	620 (46.7%)	<0.001
Diabetes mellitus with insulin		13 (4.1%)	132 (9.9%)	0.001
Dialysis		8 (2.5%)	104 (7.8%)	0.001
Cerebrovascular disease		26 (8.2%)	141 (10.6%)	0.194
Peripheral artery disease		12 (3.8%)	96 (7.2%)	0.025
Chronic lung disease		7 (2.2%)	44 (3.3%)	0.303
Hypertension		214 (67.3%)	1,001 (75.4%)	0.003
Smoking		132 (41.5%)	382 (28.7%)	<0.001
Dyslipidaemia		181 (56.9%)	925 (69.7%)	<0.001
Previous percutaneous coronary intervention		36 (11.3%)	603 (45.4%)	<0.001
Previous coronary bypass		6 (1.9%)	115 (8.7%)	<0.001
Heart failure at admission		43 (13.5%)	97 (7.3%)	<0.001
ST-elevation myocardial infarction		280 (88.1%)	0 (0%)	<0.001
Cardiogenic shock at admission		29 (9.1%)	0 (0%)	<0.001
Cardiopulmonary arrest at admission		17 (5.3%)	0 (0%)	<0.001
Intra-aortic balloon pump		51 (16.0%)	0 (0%)	<0.001
Unstable angina/ non-ST-elevation myocardial infarction		27 (8.5%)	351 (26.5%)	<0.001
Antiplatelet regimens	Aspirin	313 (98.4%)	1,303 (98.2%)	0.774
	Clopidogrel	246 (77.3%)	1,092 (82.2%)	0.043
	Prasugrel	0 (0%)	0 (0%)	
	Ticlopidine	10 (3.1%)	57 (4.3%)	0.351
	Cilostazol	5 (1.6%)	23 (1.7%)	0.842
Angio-Seal		282 (88.7%)	1,182 (89.1%)	0.840
Perclose		36 (11.3%)	145 (10.9%)	
Drug-eluting stent		183 (58.1%)	1,072 (82.7%)	<0.001
Bare metal stent		116 (36.8%)	190 (14.6%)	<0.001
Balloon angioplasty		54 (17.1%)	225 (17.3%)	0.931
Thrombectomy		178 (56.5%)	128 (9.9%)	<0.001
Rotablator		11 (3.5%)	135 (10.4%)	<0.001

Table 2. In-hospital clinical outcomes in vascular closure device users.

	Off-label users n=318 (%)	On-label users n=1,327 (%)	*p*-value
In-hospital mortality	9 (2.8%)	4 (0.3%)	<0.001
All complications	46 (14.5%)	84 (6.3%)	<0.001
Coronary dissection	9 (2.8%)	16 (1.2%)	0.033
Coronary perforation	0	5 (0.4%)	0.273
Myocardial infarction	5 (1.6%)	20 (1.5%)	0.932
Cardiogenic shock	12 (3.8%)	6 (0.5%)	<0.001
Heart failure	14 (4.4%)	5 (0.4%)	<0.001
Cerebral infarction	0 (0%)	4 (0.3%)	0.327
Intracranial haemorrhage	0 (0%)	0 (0%)	
Cardiac tamponade	4 (1.3%)	0 (0%)	<0.001
Dialysis	3 (0.9%)	3 (0.2%)	0.057
Transfusion	8 (2.5%)	18 (1.4%)	0.137
All bleeding	14 (4.4%)	30 (2.3%)	0.033
Puncture-site bleeding	4 (1.3%)	14 (1.1%)	0.755
Puncture-site haematoma	3 (0.9%)	16 (1.2%)	0.694
Peritoneal bleeding	0 (0%)	3 (0.2%)	0.396
Vascular complications	7 (2.2%)	26 (2.0%)	0.782
Gastrointestinal bleeding	0 (0%)	4 (0.3%)	0.327
Genitourinary bleeding	0 (0%)	0 (0%)	
Other bleeding	6 (1.9%)	3 (0.2%)	<0.001

Table 3. Univariate and multivariate analysis for vascular complications among vascular closure device users.

	Univariate		Multivariate	
Variable	OR (CI)	*p*-value	OR (CI)	*p*-value
Age >80	2.55 (1.17-5.55)	0.015	1.30 (0.54-3.14)	0.564
Female	4.10 (2.05-8.19)	<0.001	3.12 (1.45-6.71)	0.004
BMI <18.5	2.42 (0.72-8.14)	0.141	1.29 (0.34-4.85)	0.710
Previous myocardial infarction	1.13 (0.52-2.46)	0.753		
Previous heart failure	2.97 (1.27-7.00)	0.009	1.81 (0.67-4.89)	0.240
Diabetes mellitus	0.92 (0.46-1.84)	0.809		
Diabetes mellitus with insulin	0.32 (0.04-2.35)	0.236	0.18 (0.023-1.46)	0.109
Haemodialysis	0.42 (0.06-3.12)	0.384		
Cerebrovascular disease	0.57 (0.13-2.39)	0.432		
Peripheral artery disease	2.00 (0.69-5.80)	0.193	1.85 (0.59-5.85)	0.292
Hypertension	2.01 (0.77-5.23)	0.147	1.30 (0.48-3.53)	0.614
Smoking	0.39 (0.15-1.01)	0.044	0.56 (0.20-1.57)	0.272
Dyslipidaemia	2.22 (0.91-5.42)	0.071	2.27 (0.89-5.08)	0.060
Previous percutaneous coronary intervention	0.90 (0.44-1.84)	0.768		
Previous coronary bypass	0.81 (0.19-3.42)	0.773		
Heart failure at admission	4.24 (1.93-9.31)	<0.001	2.55 (0.96-6.77)	0.060
Cardiogenic shock at admission	1.77 (0.23-13.4)	0.576		
Intra-aortic balloon pump	3.26 (0.96-11.0)	0.080	2.42 (0.44-13.2)	0.309
Angio-Seal	0.69 (0.27-1.77)	0.442		
ST-elevation myocardial infarction	0.87 (0.33-2.27)	0.773		
Unstable angina/ non-ST-elevation myocardial infarction	1.70 (0.82-3.53)	0.153	1.35 (0.58-3.13)	0.484
Preprocedural aspirin	1.02 (1.01-1.03)	0.437		
Preprocedural clopidogrel	3.62 (0.86-15.2)	0.061	3.83 (0.88-16.7)	0.074
Off-label use	1.13 (0.48-2.62)	0.782	0.99 (0.31-3.16)	0.987

Table 4. Baseline characteristics in the on-label vascular closure device use group.

		Vascular closure device n=1,327 (%)	Manual compression n=3,856 (%)	*p*-value
Age (years)		67.8±10.6	68.5±10.3	0.028
Age >80		161 (12.1%)	508 (13.2%)	0.329
Female		275 (20.7%)	876 (22.7%)	0.132
Body mass index		24.5±3.5	24.2±3.6	0.020
Body mass index <18.5		47 (3.5%)	175 (4.5%)	0.122
Previous myocardial infarction		370 (27.9%)	1,188 (30.8%)	0.045
Previous heart failure		126 (9.5%)	486 (12.6%)	0.002
Diabetes mellitus		620 (46.7%)	1,812 (47.0%)	0.865
Diabetes mellitus with insulin		132 (9.9%)	434 (11.3%)	0.188
Dialysis		104 (7.8%)	364 (9.4%)	0.079
Creatinine (mg/dl)		0.9 [0.8, 1.1]	0.9 [0.8, 1.2]	0.956
Cerebrovascular disease		141 (10.6%)	375 (9.7%)	0.345
Peripheral artery disease		96 (7.2%)	327 (8.5%)	0.153
Chronic lung disease		44 (3.3%)	103 (2.7%)	0.222
Hypertension		1,001 (75.4%)	2,977 (77.2%)	0.188
Smoking		382 (28.8%)	1,172 (30.4%)	0.270
Dyslipidaemia		925 (69.7%)	2,620 (67.9%)	0.234
Previous percutaneous coronary intervention		603 (45.4%)	1,750 (45.4%)	0.971
Previous coronary bypass		115 (8.7%)	377 (9.8%)	0.234
Heart failure at admission		97 (7.3%)	517 (13.4%)	<0.001
Unstable angina/ non-ST-elevation myocardial infarction		351 (26.4%)	1,324 (34.3%)	<0.001
Antiplatelet regimens	Aspirin	1,303 (98.2%)	3,735 (96.9%)	0.011
	Clopidogrel	1,092 (82.2%)	2,768 (71.8%)	<0.001
	Prasugrel	0 (0.0%)	7 (0.2%)	0.120
	Ticlopidine	57 (4.3%)	153 (4.0%)	0.602
	Cilostazol	23 (1.7%)	82 (2.1%)	0.380
Angio-Seal		1,182 (89.1%)	–	
Perclose		145 (10.9%)		
Drug-eluting stent		1,072 (82.7%)	2,946 (78.6%)	0.002
Bare metal stent		190 (14.6%)	515 (13.8%)	0.410
Balloon angioplasty		225 (17.3%)	897 (23.9%)	<0.001
Thrombectomy		128 (9.9%)	339 (9.0%)	0.373
Rotablator		135 (10.4%)	170 (4.5%)	<0.001

for the use of VCD. After a propensity score matching analysis, two matched control groups were generated for on- (n=1,313) and off-label (n=313) VCD users. Baseline characteristics were similar in VCD users and controls in each group. The incidence of vascular complications did not differ with the use of VCD in the on- or off-label indication groups (2.0 vs. 2.1% in the on-label [p=0.783], and 2.2 vs. 1.6% in the off-label group [p=0.560] for VCD users vs. control) **(Table 8-Table 11, Figure 2)**.

Discussion

In the present study, 20.8% of all transfemoral PCI patients received VCD and the incidence of vascular complications was 2.1%. In this relatively lean Asian population, female gender was the only independent predictor of vascular complications with the use of VCD. When short-term in-hospital outcomes were analysed, the incidence of vascular complications did not differ among VCD users and controls in either the on-label or the off-label data set after a propensity score matching analysis. VCD users had a similar bleeding complication rate to the controls, demonstrating the safety of VCD, including its off-label use for Asian populations who are more vulnerable to bleeding. Our data also raise the question of potential off-label uses of devices in the interventional cardiology field.

Previous studies have revealed mixed results when using VCD. In 2007, the PCI registry showed that the use of VCD was associated with a reduction of the vascular complication

Table 5. Clinical outcomes in the on-label vascular closure device use group.

	Vascular closure device n=1,327 (%)	Manual compression n=3,856 (%)	*p*-value
In-hospital mortality	4 (0.3%)	23 (0.6%)	0.200
All complications	84 (6.3%)	340 (8.8%)	0.004
Coronary dissection	16 (1.2%)	51 (1.3%)	0.745
Coronary perforation	5 (0.4%)	53 (1.4%)	0.003
Myocardial infarction	20 (1.5%)	87 (2.2%)	0.098
Cardiogenic shock	6 (0.5%)	23 (0.6%)	0.543
Heart failure	5 (0.4%)	29 (0.8%)	0.144
Cerebral infarction	4 (0.3%)	11 (0.3%)	0.925
Intracranial haemorrhage	0 (0%)	1 (0.03%)	0.557
Cardiac tamponade	0 (0%)	7 (0.2%)	0.120
Dialysis	3 (0.2%)	26 (0.7%)	0.059
Transfusion	18 (1.4%)	78 (2.0%)	0.120
All bleeding	30 (2.3%)	106 (2.7%)	0.337
Puncture-site bleeding	14 (1.1%)	37 (1.0%)	0.761
Puncture-site haematoma	16 (1.2%)	46 (1.2%)	0.971
Peritoneal bleeding	3 (0.2%)	7 (0.2%)	0.750
Vascular complications	26 (2.0%)	75 (1.9%)	0.974
Gastrointestinal bleeding	4 (0.3%)	10 (0.3%)	0.799
Genitourinary bleeding	0 (0%)	1 (0.03%)	0.557
Other bleeding	3 (0.2%)	25 (0.6%)	0.070
Length of hospital stay after PCI (days)	2 [2, 3]	2 [2, 5]	<0.001

risk[24]. An analysis from the NCDR Cath PCI Registry reported that VCD reduced bleeding complications compared with manual compression[25], although patients at high risk for bleeding were less likely to receive a bleeding avoidance strategy. Another study revealed that emergent PCI could increase bleeding complications with the use of VCD compared with elective PCI[7]. In contrast,

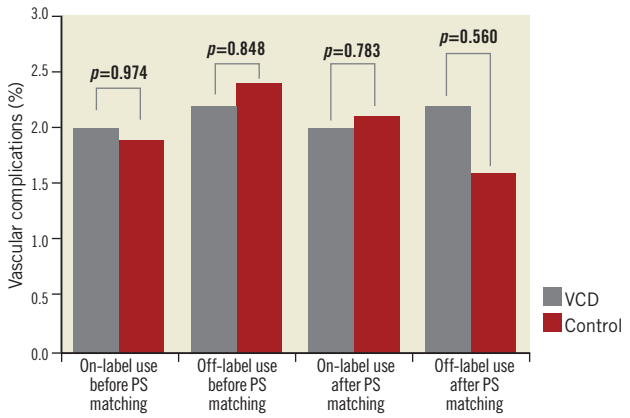

Figure 2. *Vascular complications in on- and off-label use before and after propensity score matching analysis. These graphs show similar vascular complication rates between VCD and control in each group. PS: propensity score; VCD: vascular closure device*

Table 6. Baseline characteristics in the off-label vascular closure device use group.

		Vascular closure device n=318 (%)	Manual compression n=2,400 (%)	*p*-value
Age (years)		66.5±12.7	66.6±12.2	0.958
Age >80		55 (17.3%)	371 (15.5%)	0.397
Female		74 (23.3%)	492 (20.5%)	0.253
Body mass index		23.9±3.8	23.8±3.7	0.891
Body mass index <18.5		20 (6.3%)	144 (6.0%)	0.839
Previous myocardial infarction		40 (12.6%)	279 (11.6%)	0.620
Previous heart failure		15 (4.7%)	138 (5.8%)	0.453
Diabetes mellitus		112 (35.2%)	849 (35.4%)	0.957
Diabetes mellitus with insulin		13 (4.1%)	155 (6.5%)	0.099
Dialysis		8 (2.5%)	64 (2.7%)	0.875
Creatinine (mg/dl)		0.8 [0.7, 1.0]	0.9 [0.7, 1.1]	0.064
Cerebrovascular disease		26 (8.2%)	193 (8.0%)	0.934
Peripheral artery disease		12 (3.8%)	97 (4.0%)	0.819
Chronic lung disease		7 (2.2%)	64 (2.7%)	0.625
Hypertension		214 (67.3%)	1,603 (66.8%)	0.858
Smoking		132 (41.5%)	1,068 (44.5%)	0.313
Dyslipidaemia		181 (56.9%)	1,341 (55.9%)	0.725
Previous percutaneous coronary intervention		36 (11.3%)	282 (11.8%)	0.823
Previous coronary bypass		6 (1.9%)	62 (2.6%)	0.455
Heart failure at admission		43 (13.5%)	470 (19.6%)	0.009
ST-elevation myocardial infarction		280 (88.1%)	2,120 (88.3%)	0.938
Cardiogenic shock at admission		29 (9.1%)	392 (16.3%)	0.001
Cardiopulmonary arrest at admission		17 (5.3%)	229 (9.5%)	0.014
Intra-aortic balloon pump		51 (16.0%)	717 (29.9%)	<0.001
Antiplatelet regimens	Aspirin	313 (98.4%)	2,262 (94.3%)	0.002
	Clopidogrel	246 (73.4%)	1,510 (62.9%)	<0.001
	Prasugrel	0 (0.0%)	0 (0.0%)	
	Ticlopidine	10 (3.1%)	23 (1.0%)	<0.001
	Cilostazol	5 (1.6%)	12 (0.5%)	0.023
Angio-Seal		282 (88.7%)	–	
Perclose		36 (11.3%)		
Drug-eluting stent		183 (58.0%)	1,232 (52.0%)	0.043
Bare metal stent		116 (36.7%)	981 (41.4%)	0.117
Balloon angioplasty		54 (17.1%)	441 (18.6%)	0.522
Thrombectomy		178 (56.5%)	1,405 (59.4%)	0.334
Rotablator		11 (3.5%)	35 (1.5%)	0.010

a meta-analysis in 2010 showed no increase in vascular complications, but a significantly higher risk of infection with VCD[26]. With these data, current AHA guidelines give a class III recommendation for the routine use of VCD to reduce vascular complications[5].

Table 7. Clinical outcomes in the off-label vascular closure device use group.

	Vascular closure device n=318 (%)	Manual compression n=2,400 (%)	*p*-value
In-hospital mortality	9 (2.8%)	177 (7.4%)	0.003
All complications	46 (14.5%)	491 (20.5%)	0.012
Coronary dissection	9 (2.8%)	29 (1.2%)	0.021
Coronary perforation	0 (0%)	27 (1.1%)	0.057
Myocardial infarction	5 (1.5%)	58 (2.4%)	0.347
Cardiogenic shock	12 (3.8%)	143 (6.0%)	0.114
Heart failure	14 (4.4%)	133 (5.5%)	0.399
Cerebral infarction	0 (0%)	21 (0.9%)	0.094
Intracranial haemorrhage	0 (0%)	5 (0.2%)	0.415
Cardiac tamponade	4 (1.3%)	23 (1.0%)	0.613
Dialysis	3 (0.9%)	74 (3.1%)	0.031
Transfusion	8 (2.5%)	156 (6.5%)	0.005
All bleeding	14 (4.4%)	160 (6.7%)	0.121
Puncture-site bleeding	4 (1.3%)	40 (1.7%)	0.587
Puncture-site haematoma	3 (0.9%)	19 (0.8%)	0.777
Peritoneal bleeding	0 (0%)	5 (0.2%)	0.415
Vascular complication	7 (2.2%)	57 (2.4%)	0.848
Gastrointestinal bleeding	0 (0%)	21 (0.9%)	0.094
Genitourinary bleeding	0 (0%)	7 (0.3%)	0.335
Other bleeding	6 (1.9%)	83 (3.4%)	0.139
Length of hospital stay after PCI (days)	9 [6, 15]	11 [8, 16]	<0.001

Table 8. Baseline characteristics in the on-label vascular closure device use group after a propensity matching analysis.

		Vascular closure device n=1,313 (%)	Manual compression n=1,313 (%)	*p*-value
Age (years)		67.7±10.6	68.4±9.8	0.645
Age >80		156 (11.8%)	160 (12.2%)	0.810
Female		275 (20.9%)	286 (21.8%)	0.600
Body mass index		24.5±3.5	24.4±3.6	0.558
Body mass index <18.5		46 (3.5%)	41 (3.1%)	0.586
Previous myocardial infarction		367 (28.0%)	362 (27.6%)	0.828
Previous heart failure		126 (9.6%)	134 (10.2%)	0.601
Diabetes mellitus		613 (46.7%)	616 (46.9%)	0.907
Diabetes mellitus with insulin		132 (10.1%)	152 (11.5%)	0.209
Dialysis		104 (7.9%)	111 (8.5%)	0.618
Creatinine (mg/dl)		0.9 [0.8, 1.1]	0.9 [0.7, 1.1]	0.159
Cerebrovascular disease		134 (10.2%)	127 (9.7%)	0.648
Peripheral artery disease		96 (7.3%)	91 (6.9%)	0.704
Chronic lung disease		35 (2.7%)	38 (2.9%)	0.722
Hypertension		996 (75.9%)	991 (75.5%)	0.820
Smoking		378 (28.8%)	361 (27.5%)	0.461
Dyslipidaemia		916 (69.8%)	945 (72.0%)	0.213
Previous percutaneous coronary intervention		599 (45.6%)	621 (47.3%)	0.389
Previous coronary bypass		114 (8.7%)	128 (9.7%)	0.345
Heart failure at admission		97 (7.4%)	99 (7.5%)	0.882
Unstable angina/ non-ST-elevation myocardial infarction		349 (26.6%)	329 (25.1%)	0.372
Antiplatelet regimens	Aspirin	1,289 (98.2%)	1,285 (97.9%)	0.575
	Clopidogrel	1,078 (82.1%)	1,068 (81.3%)	0.614
	Prasugrel	0 (0.0%)	3 (0.2%)	0.083
	Ticlopidine	57 (4.3%)	39 (3.0%)	0.061
	Cilostazol	22 (1.7%)	24 (1.8%)	0.766
Angio-Seal		1,171 (89.2%)	–	
Perclose		142 (10.8%)		
Drug-eluting stent		1,060 (82.6%)	1,045 (81.8%)	0.603
Bare metal stent		186 (14.5%)	171 (13.4%)	0.419
Balloon angioplasty		225 (17.5%)	290 (22.7%)	0.001
Thrombectomy		128 (10.0%)	98 (7.7%)	0.040
Rotablator		135 (10.5%)	54 (4.2%)	<0.001

In our study, a smaller proportion of critically ill patients received VCD compared to stable patients due to our system of national health insurance. Our study clarified the safety of VCD for both on- and off-label use.

To investigate the safety of off-label use and to expand labelling requires clinical trials and registry data with market forces. Off-label use would include several other devices in the interventional cardiology field. For example, the off-label use of a drug-eluting stent (DES) for coronary artery disease was common before the Food and Drug Administration concluded in 2006 that there was an increased risk of stent thrombosis with DES use, especially for off-label use[27]. After that statement, the percentage of DES use was reduced. However, registry data in 2008 showed that DES use for off-label indications did not increase the risk of adverse outcomes compared with bare metal stent use[28] and, subsequently, the percentage of DES use has recovered. Unlike DES, expanding the labelling of VCD might be difficult. Due to higher rates of vascular complications compared to Western countries[8], the use of VCD has been limited to patients who would be likely to be discharged within 48 hours in Japan. In contrast, our data showed the safety of VCD, including off-label use. However, we cannot recommend the off-label use of VCD with these data because there was a selection bias and a problem of cost. Since the VCD market would be small, compared with the market for DES use, due to the increased number of transradial PCI, it might be difficult to expand the labelling of VCD. Furthermore, several issues, such as informed consent for patients, hospital policy on whether to admit off-label use and to react in cases of complications due to device failure, manufacturer support, and operator training for use (including off-label use) would occur in off-label use[9]. Although a manufacturer may be unwilling to support the additional clinical

Table 9. In-hospital clinical outcomes in the on-label vascular closure device use group after a propensity matching analysis.

	Vascular closure device n=1,313 (%)	Manual compression n=1,313 (%)	*p*-value
In-hospital mortality	4 (0.3%)	2 (0.2%)	0.414
All complications	84 (6.4%)	115 (8.8%)	0.022
Coronary dissection	16 (1.2%)	18 (1.3%)	0.730
Coronary perforation	5 (0.4%)	22 (1.7%)	0.001
Myocardial infarction	20 (1.5%)	41 (3.1%)	0.054
Cardiogenic shock	6 (0.5%)	6 (0.5%)	1.00
Heart failure	5 (0.4%)	8 (0.6%)	0.404
Cerebral infarction	4 (0.3%)	4 (0.3%)	1.00
Intracranial haemorrhage	0 (0%)	0 (0%)	
Cardiac tamponade	0 (0%)	2 (0.2%)	0.157
Dialysis	3 (0.2%)	8 (0.6%)	0.131
Transfusion	18 (1.4%)	20 (1.5%)	0.744
All bleeding	30 (2.3%)	35 (2.7%)	0.530
Puncture-site bleeding	14 (1.1%)	13 (1.0%)	0.847
Puncture-site haematoma	16 (1.2%)	18 (1.4%)	0.730
Peritoneal bleeding	3 (0.2%)	1 (0.08%)	0.317
Vascular complication	26 (2.0%)	28 (2.1%)	0.783
Gastrointestinal bleeding	4 (0.3%)	3 (0.2%)	0.705
Genitourinary bleeding	0 (0%)	0 (0%)	
Other bleeding	3 (0.2%)	4 (0.3%)	0.705
Length of hospital stay after PCI (days)	2 [2, 3]	2 [2, 3]	<0.001

Table 10. Baseline characteristics in the off-label vascular closure device use group after a propensity score matching analysis.

		Vascular closure device n=313 (%)	Manual compression n=313 (%)	*p*-value
Age (years)		66.5±12.7	67.5±11.8	0.282
Age >80		53 (16.9%)	55 (17.6%)	0.832
Female		72 (23.0%)	66 (21.1%)	0.563
Body mass index		23.8±3.7	23.9±3.6	0.856
Body mass index <18.5		20 (6.4%)	19 (6.1%)	0.869
Previous myocardial infarction		37 (11.8%)	39 (12.5%)	0.807
Previous heart failure		15 (4.8%)	12 (3.8%)	0.555
Diabetes mellitus		112 (35.8%)	104 (33.2%)	0.501
Diabetes mellitus with insulin		13 (4.2%)	14 (4.5%)	0.844
Creatinine (mg/dl)		0.8 [0.7, 1.0]	0.9 [0.7, 1.1]	0.084
Dialysis		8 (2.6%)	9 (2.9%)	0.806
Cerebrovascular disease		26 (8.3%)	28 (8.9%)	0.776
Peripheral artery disease		12 (3.8%)	11 (3.5%)	0.832
Chronic lung disease		7 (2.2%)	3 (1.0%)	0.202
Hypertension		211 (67.4%)	212 (67.7%)	0.932
Smoking		129 (41.2%)	129 (41.2%)	1.00
Dyslipidaemia		180 (57.5%)	169 (54.0%)	0.376
Previous percutaneous coronary intervention		35 (11.2%)	39 (12.4%)	0.620
Previous coronary bypass		6 (1.9%)	7 (2.2%)	0.779
Heart failure at admission		43 (13.7%)	40 (12.8%)	0.724
ST-elevation myocardial infarction		278 (88.8%)	278 (88.8%)	1.00
Cardiogenic shock at admission		27 (8.6%)	34 (10.9%)	0.345
Cardiopulmonary arrest at admission		16 (5.1%)	16 (5.1%)	1.00
Intra-aortic balloon pump		51 (16.3%)	50 (16.0%)	0.913
Antiplatelet regimens	Aspirin	308 (98.4%)	308 (98.4%)	1.00
	Clopidogrel	241 (77.1%)	242 (77.3%)	0.924
	Prasugrel	0 (0.0%)	0 (0.0%)	
	Ticlopidine	10 (3.2%)	2 (0.6%)	0.020
	Cilostazol	5 (1.6%)	0 (0%)	0.025
Angio-Seal		277 (88.5%)	–	
Perclose		36 (11.5%)		
Drug-eluting stent		180 (58.0%)	171 (52.0%)	0.439
Bare metal stent		114 (36.7%)	120 (41.4%)	0.641
Balloon angioplasty		53 (17.1%)	44 (18.6%)	0.312
Thrombectomy		177 (56.5%)	188 (59.4%)	0.396
Rotablator		11 (3.5%)	3 (1.5%)	0.030

trials in Japan due to the associated costs[9], prospective studies to confirm the safety of VCD in various situations are needed.

For further understanding of bleeding problems, we must focus on the differences in bleeding rates in different races and genders. According to a previous study, Asian patients with coronary artery disease have higher rates of bleeding complications compared with patients in Western countries[8]. Previous studies have reported that patients with lower BMI and the elderly could lose the benefit of reducing vascular complications with the use of VCD[6,29-31]. Warren et al reported that heavier patients had more subcutaneous fat that served as a tamponade in the space around the femoral artery and/or that these patients were relatively less anticoagulated compared to thinner patients who were given approximately the same dose of heparin and antiplatelet medicines[29]. Since Asian populations are typically leaner and have higher bleeding rates than Western populations, we speculated that our data would show higher complication rates with the use of VCD in a Japanese population than those of Western countries. In contrast, we demonstrated the safety of VCD compared to manual compression, irrespective of VCD indications. Moreover, off-label use of VCD, lower BMI and age >80 were not predictors of vascular complications with VCD. However, a gender difference for vascular complications with VCD use was present in our study. Previous studies did not show a gender difference[6,29]. Our registry previously showed that female gender was an independent predictor of bleeding complications[32], and we suggest that being an Asian female might be a risk factor for vascular complications with VCD.

Table 11. Clinical outcomes in the off-label vascular closure device use group after a propensity score matching.

	Vascular closure device n=313 (%)	Manual compression n=313 (%)	*p*-value
In-hospital mortality	10 (3.2%)	16 (5.1%)	0.229
All complications	46 (14.7%)	36 (11.5%)	0.236
Coronary dissection	9 (2.9%)	4 (1.3%)	0.161
Coronary perforation	0 (0%)	4 (1.3%)	0.045
Myocardial infarction	5 (1.6%)	4 (1.3%)	0.737
Cardiogenic shock	12 (3.8%)	11 (3.5%)	0.832
Heart failure	14 (4.5%)	7 (2.2%)	0.120
Cerebral infarction	0 (0%)	1 (0.3%)	0.317
Intracranial haemorrhage	0 (0%)	0 (0%)	
Cardiac tamponade	4 (1.3%)	4 (1.3%)	1.00
Dialysis	3 (1.0%)	3 (1.0%)	1.00
Transfusion	8 (2.6%)	10 (3.2%)	0.632
All bleeding	14 (4.5%)	10 (3.2%)	0.405
Puncture-site bleeding	4 (1.3%)	3 (1.0%)	0.704
Puncture-site haematoma	3 (1.0%)	2 (0.6%)	0.653
Peritoneal bleeding	0 (0%)	0 (0%)	
Vascular complication	7 (2.2%)	5 (1.6%)	0.560
Gastrointestinal bleeding	0 (0%)	0 (0%)	
Genitourinary bleeding	0 (0%)	0 (0%)	
Other bleeding	6 (1.9%)	5 (1.6%)	0.761
Length of hospital stay after PCI (days)	9 [6, 15]	10 [8, 13]	0.048

Limitations

There were several limitations in this study. First, this was an observational clinical trial and not a randomised trial. The use of VCD depended on the decision of the operator. We could not eliminate all confounding factors or the selection bias with the propensity score matching analysis. However, a randomised trial could not have revealed the safety of off-label VCD use. Second, we did not collect data on vascular injury, such as pseudoaneurysm, fistula, dissection, and stenosis/obstruction, collagen plug distal embolisation, neurological injury, infection, delayed VCD-related bleeding complications, and time to haemostasis. However, the incidence rates of these events were low, and objective definitions were extremely difficult and can potentially distort the results of the analysis. Our definition of puncture-site bleeding included bleeding requiring transfusion and procedural intervention/surgery. Thus, pseudoaneurysm and femoral artery occlusion requiring intervention were objectively recorded as a puncture-site bleeding. Besides, we showed the length of hospital stay after PCI. Third, bivalirudin, which is thought to be a part of a bleeding avoidance strategy[33], is not available in Japan. Since we mainly use unfractionated heparin to achieve a target activated clotting time, we could investigate the pure efficacy of VCD, regardless of the pharmacological effects in other studies[25]. Finally, we did not have data on preprocedural oral anticoagulation, liver function, size of the sheaths, and the operators' skill. These factors would affect vascular complications[5,6,29].

Conclusions

In conclusion, the use of VCD showed a similar rate of bleeding complications compared with the control, including in patients with off-label use. Although we must remain cautious about the use of VCD for female patients, our results demonstrate the safety of using VCD for Japanese patients. More studies are necessary to confirm the safety of VCD in different scenarios.

Impact on daily practice

Although Japanese patients are vulnerable to bleeding and the use of vascular closure devices was restricted to stable patients, we revealed the safety of vascular closure devices for on-label and off-label use in a large multicentre registry. Moreover, we found that female gender was an independent predictor of vascular complications with the use of vascular closure devices. Further studies, such as randomised studies, are needed to confirm the safety of VCD in different scenarios and to expand the labelling.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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