Transradial vs. Transfemoral Percutaneous Coronary Intervention in Patients With or Without High Bleeding Risk Criteria

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Background: The transradial approach is reportedly associated with reduced bleeding complications and mortality after percutaneous coronary intervention (PCI). It is unknown whether the clinical benefits of transradial vs. transfemoral PCI differ between high bleeding risk (HBR) and non-HBR patients.

Methods and Results: After excluding patients with acute myocardial infarction, dialysis, and a transbrachial approach from the 13,087 patients undergoing first PCI in the CREDO-Kyoto Registry Cohort-2, 6,828 patients were eligible for this study. Patients were divided into 2 groups according to bleeding risk based on Academic Research Consortium HBR criteria, and then divided into a further 2 groups according to access site, radial or femoral: HBR-radial, $n=1,054$ (38.3%); HBR-femoral, $n=1,699$ (61.7%); non-HBR-radial, $n=1,682$ (41.3%); and non-HBR-femoral, $n=2,393$ (58.7%). In the HBR group, the 30-day incidence and adjusted risk for major bleeding (1.9% vs. 4.7% [$P<0.001$]; adjusted hazard ratio [aHR] 0.44, 95% confidence interval [CI] 0.26–0.71 [$P<0.001$]) and all-cause death (0.3% vs. 0.9% [$P=0.04$]; aHR 0.30, 95% CI 0.07–0.93 [$P=0.04$]) were significantly lower in the radial than femoral group. There were no significant differences in the 30-day incidence and adjusted risk for major bleeding (0.5% vs. 1.0% [$P=0.09$]; aHR 0.68, 95% CI 0.30–1.45 [$P=0.33$]) or all-cause death (0.1% vs. 0.1% [$P=0.96$]; aHR 1.51, 95% CI 0.19–9.54 [$P=0.67$]) between the radial and femoral approaches in the non-HBR group.

Conclusions: Compared with transfemoral PCI, transradial PCI was associated with lower risk for 30-day major bleeding and mortality in HBR but not non-HBR patients.

Key Words: High bleeding risk; Transfemoral; Transradial

According to several randomized trials and meta-analyses, the transradial approach is associated with reduced bleeding complications and even reduced mortality after percutaneous coronary intervention (PCI).^{1–4} Thus, transradial access has been recommended as the standard approach for PCI in the guidelines of the European Heart Society and Japanese Circulation Society, as well as the scientific statement of the American Heart Association.^{5–7} The benefits associated with transradial access were mostly related to a reduction in major bleeding complications.^{8–10} These beneficial effects may particularly be prominent in patients with a high bleeding risk (HBR). However,

it is unknown whether the clinical benefits of transradial relative to transfemoral PCI differ between HBR and non-HBR patients. Hence, in this study we examined the effects of transradial vs. transfemoral PCI on clinical outcomes in patients with or without HBR, as defined by the Academic Research Consortium (ARC) HBR criteria,¹¹ in a large Japanese database of patients undergoing first coronary revascularization.

Methods

The research protocol was approved by the relevant review

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Table 1. Prevalence of Major and Minor Academic Research Consortium HBR Criteria in the Study Population Overall and Stratified According to Access Site (Femoral or Radial)

	Entire cohort (n=6,828)	Radial group (n=2,736)	Femoral group (n=4,092)
Major criteria			
Long-term anticoagulation	488 (7.1)	189 (6.9)	299 (7.3)
Severe CKD ^A	255 (3.7)	67 (2.4)	188 (4.6)
Severe anemia ^B	657 (9.6)	213 (7.8)	444 (10.9)
Thrombocytopenia ^C	78 (1.1)	23 (0.8)	55 (1.3)
Liver cirrhosis	166 (2.4)	64 (2.3)	102 (2.5)
Prior hemorrhagic stroke	113 (1.7)	43 (1.6)	70 (1.7)
Minor criteria			
Age ≥75 years	2,114 (31.0)	859 (31.4)	1,255 (30.7)
Moderate CKD ^A	2,246 (32.9)	851 (31.1)	1,395 (34.1)
Mild anemia ^B	1,365 (20.0)	548 (20.0)	817 (20.0)
Prior ischemic stroke	689 (10.1)	273 (10.0)	416 (10.2)
HBR	2,753 (40.3)	1,054 (38.5)	1,699 (41.5)
No-HBR	4,075 (59.7)	1,682 (61.5)	2,393 (58.5)
1 minor criterion	2,201 (32.2)	845 (30.9)	1,356 (33.1)
No criteria	1,874 (27.4)	837 (30.6)	1,037 (25.3)

Data are presented as n (%). ^ASevere chronic kidney disease (CKD) was defined as estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m² and not on dialysis; moderate CKD was defined as an eGFR of 30–59 mL/min/1.73 m².

^BSevere anemia was defined as hemoglobin (Hb) <11 g/dL; mild anemia was defined as Hb 11–12.9 g/dL for men and 11–11.9 g/dL for women. ^CThrombocytopenia was defined as a platelet count <100×10⁹/L. HBR, high bleeding risk.

boards or ethics committees in all participating centers. Because study enrollment was retrospective, the need for written informed consent from patients was waived; however, patients who declined study participation when contacted for follow-up were excluded. This strategy is concordant with the guidelines for epidemiological studies issued by the Ministry of Health, Labor and Welfare of Japan, and the Kyoto University Graduate School and Faculty of Medicine, Ethics Committee (Reference no. e42).

The Coronary Revascularization Demonstrating Outcome study in Kyoto (CREDO-Kyoto) PCI Registry Cohort-2 is a multicenter registry that enrolled consecutive patients undergoing first coronary revascularization procedures in 26 Japanese centers between January 2005 and December 2007 (Supplementary Appendix 1).¹² The design and patient enrollment of the CREDO-Kyoto PCI Registry Cohort-2 have been described elsewhere.¹² In the present study, we compared 30-day clinical outcomes between transradial and transfemoral PCI stratified by ARC-HBR.

During the 3-years enrollment period, 13,144 patients underwent PCI as their first coronary revascularization procedure. The 57 patients who declined to participate in the study were excluded, leaving 13,087 patients in the PCI arm of the registry. A further 4,729 patients with acute myocardial infarction and 397 patients on hemodialysis were excluded because the femoral approach was mostly selected in these patients. In addition, 1,099 patients who were treated via the brachial artery and 34 patients with missing information on the arterial access site were excluded. Consequently, the current study population consisted of 6,828 patients; this is the same study population, in which we previously compared clinical outcomes between transradial and transfemoral PCI.¹³

The study population was divided into 2 groups based on ARC HBR criteria.¹¹ In the present study we modified the ARC HBR definitions because some of the criteria

were not exactly captured in the CREDO-Kyoto Registry; specifically, oral anticoagulant medication at discharge from the index hospitalization was regarded as major criterion for long-term oral anticoagulation, liver cirrhosis was considered a major criterion regardless of the presence of portal hypertension, malignancy was excluded from the criteria for HBR because we did not have information as to whether it was active or not, history of hemorrhagic stroke was regarded as a major criterion but we did not have information on recent traumatic intracranial hemorrhage, and a history of all-ischemic stroke was regarded as a minor criterion because we did not have information on its timing. Information regarding a previous history of spontaneous bleeding requiring hospitalization or transfusion, bleeding diathesis, brain arteriovenous malformation, planned major surgery, recent major trauma or surgery, and the use of non-steroidal anti-inflammatory drugs or steroids was not captured in the registry, and so these criteria were regarded as absent. There were missing values for serum creatinine in 61 patients, platelet count in 45 patients, and hemoglobin in 58 patients, and these patients were regarded as not having those HBR criteria (e.g., chronic kidney disease [CKD], thrombocytopenia, and anemia). In the present analysis, patients were regarded as HBR if they had at least 1 major criterion (e.g., severe CKD, thrombocytopenia, severe anemia, liver cirrhosis, prior hemorrhagic stroke, or anticoagulation) or ≥2 minor criteria (e.g., age ≥75 years, mild anemia, prior ischemic stroke, or moderate CKD; Table 1).¹⁴ Patients in the HBR and non-HBR groups were divided into a further 2 groups according to access site, radial or femoral (see Figure 1): HBR-radial, n=1,054 (38.3%); HBR-femoral, n=1,699 (61.7%); non-HBR-radial, n=1,682 (41.3%); and non-HBR-femoral, n=2,393 (58.7%). The clinical outcomes at 30 days after PCI were compared between the radial and femoral groups in patients with or without ARC-defined HBR.

Scheduled staged PCI procedures performed during the index hospitalization or within 3 months of the initial procedure were not regarded as follow-up events and were included in the index procedure. The arterial access site of patients who underwent staged PCI procedures was evaluated only at the time of the first PCI procedure. When the initial access site was changed to another site due to arterial puncture failure, only the final access site was recorded in the case report form, and patients were classified based on the final access site. The recommended antiplatelet regimen included aspirin (≥ 81 mg daily), which was administered indefinitely, and thienopyridine (200 mg ticlopidine or 75 mg clopidogrel daily), which was administered for at least 3 months. Unfractionated heparin was used as an antithrombotic agent during PCI, with the dose based on local protocols in the participating centers. No patients were treated with a glycoprotein IIb/IIIa inhibitor or bivalirudin.

Baseline clinical characteristics have been reported elsewhere.¹² Complex PCI was defined as a procedure with at least 1 of the following angiographic characteristics: 3 vessels treated, ≥ 3 stents implanted, ≥ 3 lesions treated, bifurcation with 2 stents implanted, total stent length > 60 mm, or chronic total occlusion as the target lesion.¹⁵

The primary endpoint was major bleeding, defined as Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded coronary arteries (GUSTO) moderate/severe bleeding, at 30 days at the puncture site and/or a non-puncture site.¹⁶ Procedural bleeding, such as hematoma and retroperitoneal bleeding, was defined as puncture site bleeding, although hematoma size was not measured. Non-puncture site bleeding was classified into the following 5 categories without overlap according to the location

and cause of bleeding: intracranial, gastrointestinal, related to surgery, related to PCI, and others. Non-puncture site bleeding related to PCI was defined as PCI procedural bleeding not involving the puncture site (e.g., coronary artery perforation).

Secondary endpoints included death, cardiac death, myocardial infarction, stroke, target lesion revascularization, coronary artery bypass grafting, any coronary revascularization, and major adverse cardiac events (MACE), which consisted of a composite of death, myocardial infarction, or stroke. Death was regarded as cardiac in origin unless obvious non-cardiac causes could be identified. Any death during the index hospitalization was regarded as a cardiac death. Myocardial infarction was defined according to the Arterial Revascularization Therapy Study.¹⁷ Within 1 week of the index procedure, only Q-wave myocardial infarction was adjudicated as myocardial infarction. Stroke during follow-up was defined as ischemic or hemorrhagic stroke requiring hospitalization with symptoms lasting > 24 h. The definitions of endpoints have been reported elsewhere.^{12,13} All clinical events were adjudicated by an independent clinical event committee.

Demographic, angiographic, and procedural data were collected from hospital charts or databases in each participating center according to prespecified definitions by experienced clinical research coordinators in the study management center (**Supplementary Appendix 2**). Follow-up data on clinical events was then collected from hospital charts in the participating centers or from letters and/or telephone calls to patients or referring physicians. The follow-up interval was calculated from the day of the index PCI procedure.

Statistical Analysis

Categorical variables are expressed as numbers and percentages and were compared using Chi-squared tests. Continuous variables are expressed as the mean±SD or median and interquartile range (IQR), and were compared using Student's t-test or the Wilcoxon rank-sum test depending on distribution. Cumulative incidence was estimated by the Kaplan-Meier method, and the significance of differences was assessed using the log-rank test. The risk of clinical events in the radial group compared with the femoral group is expressed as hazard ratios (HRs) and 95% confidence intervals (CIs). HRs were estimated using the Cox proportional hazard models adjusted for 4 clinically relevant factors, namely age (≥75 years), sex, urgent procedure, and complex PCI based on clinical relevance (Table 1).

All statistical analyses were conducted using JMP 14.0 (SAS Institute, Cary, NC, USA). All reported P-values are 2-tailed, and P<0.05 was considered significant.

Results

There were substantial differences in baseline characteristics and medications between the radial and femoral groups, and these differences were generally consistent in the HBR and non-HBR groups. Compared with the radial group, the femoral group included more women, as well as patients with urgent procedures, unstable angina, and more often with comorbidities, such as heart failure and prior myocardial infarction. Among HBR patients, the radial group more often had diabetes, severe CKD, and severe anemia. Peripheral vascular disease was more common in the radial than femoral group. In terms of angiographic and procedural characteristics, the femoral group had significantly more patients with complex characteristics than the radial group. Sheath size and the amount of contrast were greater in the femoral than radial group. Baseline medications were also different between the 2 groups (Table 2).

Among HBR patients, the 30-day incidence of major bleeding was significantly lower in the radial than femoral

Table 2. Baseline Characteristics and Medications of Patients With a HBR and Non-HBR Patients Stratified According to Access Site (Femoral or Radial)

	HBR (n=2,753)			Non-HBR (n=4,075)		
	Radial group (n=1,054)	Femoral group (n=1,699)	P-value	Radial group (n=1,682)	Femoral group (n=2,393)	P-value
Clinical characteristics						
Age (years)	74.8±8.2	74.2±9.1	0.07	64.3±9.4	64.6±9.3	0.3
Age ≥75 years ^A	660 (63)	977 (58)	0.008	199 (12)	278 (12)	0.83
Men ^A	718 (68)	1,084 (64)	0.02	1,337 (79)	1,756 (73)	<0.001
BMI (kg/m ²)	23.1±3.4	23.2±3.5	0.63	24.5±3.4	24.4±3.3	0.35
BMI <25.0 kg/m ²	780 (74)	1,215 (72)	0.15	1,035 (62)	1,453 (61)	0.6
Urgent procedure ^A	39 (3.7)	143 (8.4)	<0.001	73 (4.3)	252 (11)	<0.001
Unstable angina	70 (6.6)	222 (13)	<0.001	125 (7.4)	328 (14)	<0.001
Hypertension	930 (88)	1,501 (88)	0.93	1,346 (80)	1,977 (83)	0.04
Diabetes	389 (37)	729 (43)	0.002	641 (38)	920 (38)	0.83
On insulin therapy	106 (10)	194 (11)	0.27	109 (6.5)	167 (7.0)	0.53
Current smoker	206 (20)	349 (21)	0.53	516 (31)	784 (33)	0.16
Heart failure	202 (19)	450 (26)	<0.001	87 (5.2)	176 (7.4)	0.005
NYHA Class IV	27 (2.6)	68 (4.0)	0.04	11 (0.7)	19 (0.8)	0.61
Prior myocardial infarction	156 (15)	411 (24)	<0.001	145 (8.6)	343 (14)	<0.001
Prior stroke	240 (24)	389 (23)	0.94	66 (3.9)	84 (3.5)	0.49
Prior hemorrhagic stroke	43 (4.1)	70 (4.1)	0.96	0 (0.0)	0 (0.0)	–
Prior ischemic stroke	207 (20)	332 (20)	0.95	66 (3.9)	84 (3.5)	0.49
Peripheral vascular disease	166 (16)	176 (10)	<0.001	107 (6.4)	116 (4.9)	0.04
Atrial fibrillation	158 (15)	257 (15)	0.92	53 (3.2)	63 (2.6)	0.33
eGFR (mL/min/1.73 m ²)	56.4±18.1	53.6±19.9	<0.001	73.8±15.9	73.1±30.1	0.41
Moderate CKD ^B	594 (56)	969 (57)	0.73	257 (15)	426 (18)	0.03
Severe CKD ^B	67 (6.4)	188 (11)	<0.001	0 (0.0)	0 (0.0)	–
Mild anemia ^C	419 (40)	615 (36)	0.06	129 (7.7)	202 (8.4)	0.37
Severe anemia ^C	213 (20)	444 (26)	<0.001	0 (0.0)	0 (0.0)	–
Platelet count <100×10 ⁹ /L	23 (2.2)	55 (3.2)	0.1	0 (0.0)	0 (0.0)	–
LVEF	61.5±12.8	57.3±14.6	<0.001	64.4±10.2	61.6±11.7	<0.001
LVEF ≤40%	73 (8.1)	211 (15)	<0.001	45 (3.1)	113 (5.5)	<0.001
Mitral regurgitation grade 3/4	62 (5.9)	118 (7.0)	0.27	24 (1.4)	67 (2.8)	0.004
COPD	44 (4.2)	90 (5.3)	0.18	57 (3.4)	84 (3.5)	0.83
Liver cirrhosis	64 (6.1)	102 (6.0)	0.94	0 (0.0)	0 (0.0)	–
Malignancy	166 (16)	234 (14)	0.15	117 (7.0)	176 (7.4)	0.63

(Table 2 continued the next page.)

	HBR (n=2,753)			Non-HBR (n=4,075)		
	Radial group (n=1,054)	Femoral group (n=1,699)	P-value	Radial group (n=1,682)	Femoral group (n=2,393)	P-value
Procedural characteristics						
No. target lesions	1 [1–2], 1.46±0.72	1 [1–2], 1.54±0.82	0.009	1 [1–2], 1.40±0.69	1 [1–2], 1.53±0.79	<0.001
No. target lesions ≥3	98 (9.3)	189 (11)	0.13	131 (7.8)	277 (12)	<0.001
Multivessel disease	603 (57)	1,137 (67)	<0.001	805 (48)	1,412 (59)	<0.001
Target of proximal LAD	582 (55)	1,063 (63)	<0.001	979 (58)	1,491 (62)	0.008
Target of unprotected LMCA	33 (3.1)	86 (5.1)	0.02	30 (1.8)	94 (3.9)	<0.001
Target of CTO	79 (7.5)	379 (22)	<0.001	111 (6.6)	619 (26)	<0.001
Target of bifurcation	315 (30)	640 (38)	<0.001	551 (33)	934 (39)	<0.001
Side-branch stenting	45 (4.3)	115 (6.8)	0.006	75 (4.5)	159 (6.6)	0.003
Target of triple vessel disease	49 (4.7)	102 (6.0)	0.13	67 (4.0)	137 (5.7)	0.01
Total no. stents	1 [1–2], 1.89±1.23	2 [1–3], 2.13±1.42	<0.001	1 [1–2], 1.75±1.15	2 [1–3], 2.01±1.34	<0.001
Total no. stents ≥3	224 (21)	449 (26)	0.002	300 (18)	589 (25)	<0.001
Total stent length >28mm	507 (50)	930 (58)	<0.001	708 (44)	1,229 (55)	<0.001
Total stent length >60mm	176 (17)	380 (22)	<0.001	240 (14)	505 (21)	<0.001
Minimum stent size <3.0mm	499 (50)	850 (53)	0.05	679 (43)	1,090 (48)	<0.001
Procedural success of PCI	1,039 (99)	1,633 (96)	<0.001	1,660 (99)	2,313 (97)	<0.001
DES use	693 (66)	1,140 (67)	0.47	1,135 (67)	1,539 (64)	0.04
Sheath size (Fr)	6.08±0.43	6.75±0.58	<0.001	6.13±0.44	6.71±0.57	<0.001
Sheath size >6 Fr	132 (13)	1,181 (70)	<0.001	280 (17)	1,611 (67)	<0.001
Contrast amount (mL)	150 [100–200]	187 [130–260]	<0.001	150 [110–208]	195 [140–260]	<0.001
Contrast amount >175mL	342 (32)	872 (51)	<0.001	620 (37)	1,274 (53)	<0.001
Staged PCI	182 (17)	374 (22)	0.003	250 (15)	566 (24)	<0.001
Complex PCI ^a	294 (28)	735 (43)	<0.001	419 (25)	1,052 (44)	<0.001
Medication at hospital discharge						
Thienopyridine	1,027 (97)	1,672 (98)	0.07	1,647 (98)	2,351 (98)	0.45
Ticlopidine	880 (83)	1,505 (89)	<0.001	1,432 (85)	2,140 (89)	<0.001
Clopidogrel	146 (14)	161 (9.5)	<0.001	212 (13)	203 (8.5)	<0.001
Aspirin	1,026 (97)	1,673 (98)	0.04	1,664 (99)	2,372 (99)	0.53
Cilostazol	99 (9.4)	188 (11)	0.16	149 (8.9)	271 (11)	0.01
Warfarin	189 (18)	299 (18)	0.82	0 (0.0)	0 (0.0)	–
Statins	481 (46)	786 (46)	0.75	917 (55)	1,408 (59)	0.006
β-blockers	273 (26)	555 (33)	<0.001	348 (21)	587 (25)	0.004
ACEI/ARB	602 (57)	991 (58)	0.53	714 (42)	1,196 (50)	<0.001
Proton pump inhibitors	368 (22)	516 (22)	0.81	269 (16)	439 (18)	0.05
H ₂ receptor blockers	259 (25)	385 (23)	0.25	253 (24)	448 (26)	0.17

Continuous variables are expressed as the mean±SD or median [(interquartile range)]. Categorical variables are expressed as n (%). Complex percutaneous coronary intervention (PCI) was defined as a procedure with at least 1 of the following procedural characteristics: 3 vessels treated, ≥3 stents implanted, ≥3 lesions treated, bifurcation with 2 stents implanted, total stent length >60mm, or chronic total occlusion as the target lesion.¹¹ ^aRisk-adjusting variables selected for the Cox proportional hazard models. ^bSevere CKD was defined as eGFR <30 mL/min/1.73 m² and not on dialysis; moderate CKD was defined as an eGFR of 30–59 mL/min/1.73 m². ^cSevere anemia was defined as Hb <11 g/dL; mild anemia was defined as Hb 11–12.9 g/dL for men and 11–11.9 g/dL for women. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CTO, chronic total occlusion; DES, drug-eluting stent; HBR, high bleeding risk; LAD, left anterior descending; LMCA, left main coronary artery; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association. Other abbreviations as in Table 1.

group (1.9% vs. 4.7%; $P<0.001$; **Table 3; Figure 2A**). After adjusting for confounders, the lower risk of the radial relative to the femoral group for major bleeding remained highly significant (adjusted HR 0.44; 95% CI 0.26–0.71; $P<0.001$; **Figure 3**). The cumulative incidence of puncture site and non-puncture site bleeding was also significantly lower in the radial than femoral group (0.5% vs. 1.7% [$P=0.002$] and 1.4% vs. 3.0% [$P=0.006$], respectively; **Table 3; Figure 2A**). The excess non-puncture site bleeding in the femoral compared with radial group was primarily driven by the excess bleeding related to surgery and the PCI. The incidence of bleeding related to surgery was significantly higher in the femoral than radial group (**Table 3**). Of the 16 patients

with bleeding related to surgery, 9 (57%) had bleeding associated with coronary artery bypass grafting (CABG). The adjusted risks of the radial relative to the femoral group for puncture site and non-puncture site bleeding remained significant (adjusted HRs 0.29 [95% CI 0.10–0.69; $P=0.004$] and 0.53 [95% CI 0.29–0.93; $P=0.03$], respectively; **Figure 3**). The incidence of all-cause death and cardiac death was significantly lower in the radial than femoral group (0.3% vs. 0.9% [$P=0.04$] and 0.2% vs. 0.7% [$P=0.047$], respectively; **Table 3**). The adjusted risks of the radial relative to the femoral group for all-cause death and cardiac death also remained significant (adjusted HRs 0.30 [95% CI 0.07–0.93; $P=0.04$] and 0.25 [95% CI 0.04–0.93; $P=0.04$], respectively;

Table 3. Clinical Outcomes at 30 Days After PCI in Patients With a HBR and Non-HBR Patients Stratified According to Access Site (Femoral or Radial)

	Cumulative 30-day incidence ^A		Unadjusted HR (95% CI) ^B	P-value
	Radial group	Femoral group		
HBR (n=2,753)	n=1,054	n=1,699		
GUSTO moderate/severe bleeding	20 (1.9)	80 (4.7)	0.40 (0.24–0.64)	<0.001
Puncture site bleeding	5 (0.5)	29 (1.7)	0.28 (0.09–0.65)	0.002
Non-puncture site bleeding	15 (1.4)	51 (3.0)	0.47 (0.26–0.82)	0.006
Gastrointestinal bleeding	10 (1.0)	15 (1.0)	1.06 (0.46–2.34)	0.88
Intracranial bleeding	1 (0.1)	5 (0.3)	0.31 (0.02–1.95)	0.24
Bleeding related to PCI	2 (0.2)	9 (0.5)	0.35 (0.05–1.38)	0.14
Bleeding related to surgery	2 (0.2)	14 (0.9)	0.23 (0.04–0.81)	0.02
All-cause death	3 (0.3)	15 (0.9)	0.32 (0.07–0.98)	0.04
Cardiac death	2 (0.2)	12 (0.7)	0.27 (0.04–0.99)	0.047
Myocardial infarction	17 (1.6)	23 (1.4)	1.19 (0.63–2.22)	0.58
Stroke	5 (0.5)	11 (0.7)	0.73 (0.23–2.01)	0.56
Death/myocardial infarction/stroke	22 (2.1)	45 (2.7)	0.79 (0.47–1.30)	0.36
Target lesion revascularization	15 (1.4)	30 (1.8)	0.81 (0.42–1.47)	0.49
Coronary artery bypass grafting	3 (0.3)	15 (0.9)	0.32 (0.07–0.97)	0.04
Any coronary revascularization	18 (1.7)	40 (2.4)	0.72 (0.41–1.24)	0.25
Non-HBR (n=4,075)	n=1,682	n=2,393		
GUSTO moderate/severe bleeding	9 (0.5)	24 (1.0)	0.53 (0.23–1.11)	0.09
Puncture site bleeding	0 (0.0)	12 (0.5)	NA	0.004
Non-puncture site bleeding	9 (0.5)	12 (0.5)	1.07 (0.44–2.53)	0.88
Gastrointestinal bleeding	1 (0.1)	4 (0.1)	0.36 (0.02–2.40)	0.31
Intracranial bleeding	1 (0.1)	1 (0.04)	1.42 (0.06–36.0)	0.8
Bleeding related to PCI	2 (0.1)	2 (0.1)	1.42 (0.17–11.8)	0.73
Bleeding related to surgery	5 (0.3)	2 (0.1)	3.56 (0.77–24.8)	0.11
All-cause death	2 (0.1)	3 (0.1)	0.95 (0.13–5.74)	0.96
Cardiac death	2 (0.1)	3 (0.1)	0.95 (0.13–5.74)	0.96
Myocardial infarction	17 (1.0)	16 (0.7)	1.41 (0.76–3.02)	0.23
Stroke	1 (0.1)	10 (0.4)	0.14 (0.01–0.74)	0.02
Death/myocardial infarction/stroke	19 (1.1)	28 (1.2)	0.97 (0.53–1.72)	0.91
Target lesion revascularization	19 (1.1)	44 (1.9)	0.61 (0.35–1.04)	0.07
Coronary artery bypass grafting	7 (0.4)	21 (0.9)	0.48 (0.19–1.07)	0.07
Any coronary revascularization	23 (1.4)	53 (2.2)	0.62 (0.37–0.99)	0.047

^AThe number of patients with the event was counted at 30 days. Cumulative incidence was estimated by the Kaplan-Meier method censored at 30 days. Data for cumulative incidence is given as n (%). ^BUnadjusted hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated by the Cox proportional hazard model. GUSTO, Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries; HBR, high bleeding risk; NA, not applicable; PCI, percutaneous coronary intervention.

Figure 3).

Among non-HBR patients, the 30-day incidence of major bleeding was low and not significantly different between the radial and femoral groups (0.5% vs. 1.0%, respectively; $P=0.09$; **Table 3; Figure 2B**). The incidence of puncture site bleeding was significantly lower in the radial than femoral group (0.0% vs. 0.5%; $P=0.004$; **Table 3; Figure 2B**). The incidence of non-puncture site bleeding was not significantly different between the radial and femoral groups (0.5% vs. 0.5%; $P=0.88$; **Table 3; Figure 2B**). After adjusting for confounders, the risk of the radial relative to the femoral group for major bleeding remained non-significant (adjusted HR 0.68; 95% CI 0.30–1.45; $P=0.33$; **Figure 3**). The cumulative incidence of all-cause death was low and not significantly different between the 2 groups (0.1% vs. 0.1%; $P=0.96$; **Table 3**). The incidence of stroke was significantly lower in the radial than femoral group, but the adjusted risk of the radial relative to the femoral group for

stroke was no longer significant (**Table 3; Figure 3**). There were no significant interactions between HBR or non-HBR status and the approach site for any clinical event (**Figure 3**). The results for other endpoints, such as target lesion revascularization, CABG, and any coronary revascularization, are given in **Table 3**.

Discussion

The main findings of the present observational study comparing the transradial and transfemoral approaches for PCI stratified by bleeding risk were as follows: (1) compared with the transfemoral approach, the transradial approach was associated with a significantly lower risk for 30-day major bleeding in HBR but not non-HBR patients, although there was no significant interaction between the bleeding risk and the access site; and (2) the transradial approach was associated with lower mortality in HBR patients.

Bleeding complications related to PCI procedures are associated with adverse clinical outcomes, including myocardial infarction, stroke, and death.^{18–20} Furthermore, periprocedural bleeding is the strongest independent predictor of mortality, with a greater effect on mortality than periprocedural myocardial infarction.^{21,22} Therefore, it is crucially important to prevent periprocedural bleeding complications to improve clinical outcomes after PCI. In a meta-analysis of randomized trials, Ferrante et al reported that radial access was associated with a significantly lower risk for all-cause mortality (odds ratio [OR] 0.71; 95% CI 0.59–0.87; $P=0.001$), major bleeding (OR 0.53; 95% CI 0.42–0.65; $P<0.001$), and major vascular complications (OR 0.23, 95% CI 0.16–0.35; $P<0.001$).⁴ Mamas et al reported that the

transradial approach was associated with reduced 30-day mortality and bleeding, and that the magnitude of this effect was related to baseline bleeding risk calculated by using modified Mehran bleeding scores (MMRS): low (<10) MMRS, OR 0.69, 95% CI 0.56–0.85, $P=0.001$; moderate (10–14) MMRS, OR 0.67, 95% CI 0.57–0.79, $P<0.0001$; high (15–19) MMRS, OR 0.49, 95% CI 0.42–0.57, $P<0.0001$; and very high (≥ 20) MMRS, OR 0.46, 95% CI 0.36–0.59, $P<0.0001$.²³ In a previous study we compared clinical outcomes for the transradial and transfemoral approaches in the overall population of the present study.¹³ The 30-day incidence of access site bleeding was significantly lower in the radial than femoral group, whereas the 30-day incidence of all-cause death was not significantly different between

the 2 groups. In the present study, using the ARC-HBR criteria, the absolute difference in 30-day major bleeding rate between the transradial and transfemoral approaches was much greater in HBR than non-HBR patients, and the transradial approach was also associated with lower mortality in HBR patients. Therefore, the clinical benefits of the transradial approach seem to be greater in HBR than non-HBR patients, suggesting that the transradial approach is preferred particularly in HBR patients.

Andó et al reported that radial access was associated with a reduced risk of acute kidney injury (AKI) compared with femoral access (OR 0.87; 95% CI 0.77–0.98; $P=0.0181$).²⁴ Pickering et al also reported that acute coronary syndrome-associated AKI was associated with a more than 3-fold increase in 30-day mortality (relative risk 4.1; 95% CI 3.3–5.0).²⁵ Because moderate or severe CKD is included in the ARC HBR criteria, transradial PCI may reduce the risk of death, especially for those with renal dysfunction, by reducing bleeding complications and AKI.

Mamas et al reported that baseline bleeding risk was not associated with selection of access site in the British Cardiovascular Intervention Society database.²³ In line with that

report, the transradial approach was less often chosen in HBR patients than non-HBR patients in the present study. One of the disadvantages of transradial PCI is the limited guiding catheter size. Indeed, sheath size was significantly larger in the femoral than radial group in the present study. A large guiding catheter provides improved backup support and enables the use of bulky devices, which could be one of the reasons for the higher prevalence of complex lesions in the femoral than radial group. Patients with high thrombotic risks undergoing complex PCI also had a high bleeding risk, leading to the high prevalence of the transfemoral approach in HBR patients.^{26–28} However, the Glidesheath Slender (Terumo, Tokyo, Japan), which combines an inner diameter compatible with a 7-Fr guiding catheter with an outside diameter close to current 6-Fr sheaths, sheath-less catheters, and guide extension catheters, is available in current PCI practice. Therefore, it is getting easier to select the transradial approach even in patients undergoing complex PCI. Another disadvantage of transradial PCI was the higher rate of arterial access failure.^{29,30} However, Nguyen et al reported that ultrasound-guided puncture reduced mean access time (93 vs. 111 s; $P=0.009$), the mean number

of attempts (1.47 vs. 1.9; $P < 0.0001$), and the rate of difficult accesses (4.5% vs. 9.2%; $P = 0.0007$) and improved first-pass access (73% vs. 59.7%; $P < 0.0001$).³¹ It would be beneficial to implement the transradial approach more widely in HBR patients requiring complex PCI.

The present study has several limitations. First, the present study was an observational study with limitations inherent to such a study design, including selection bias and unmeasured confounders. Despite substantial differences in the baseline characteristics between the radial and femoral groups, there were limitations in the sample size and the number of events to fully adjust the effects of confounders. Furthermore, we cannot rule out the possibility of an effect of selection bias and residual confounding. The lower incidence of mortality or non-puncture site bleeding in the radial compared with femoral group among HBR patients may be related to differences in patient characteristics rather than to differences in the approach site per se, thus suggesting the presence of residual confounding. Therefore, caution is warranted in interpreting the results of the present study, especially the lower mortality in the radial than femoral group, although the benefit of transradial PCI in the present study is consistent with previous studies.^{2,4} Second, when the initial approach site was changed to another site due to arterial puncture failure, only the final approach site was recorded in the case report form. Thus, we could not evaluate the effect of puncture failure and conversion of approach site. The experience of operators for transradial PCI was unknown. In addition, we did not have information on the long-term patency of the radial artery. Moreover, only the first PCI procedure in each patient was evaluated. Some patients with staged PCI procedures may have undergone both transfemoral and transradial procedures. Third, clinical practice, including selection of the arterial approach site, coronary device, and medical treatment, has changed over time from the period when the present study was conducted to current daily clinical practice. None of the patients in the present study used prasugrel or a non-vitamin K oral anticoagulant, which are used in current clinical practice. The antithrombotic drugs used at the time of the procedure were unknown. Coronary devices such as the Glidesheath Slender and guide extension catheters were not available during the enrollment period of this study. Fourth, we did not have information regarding the mechanical support devices used, such as intra-aortic balloon pumps and extracorporeal membrane oxygenation. However, the number of patients using mechanical support devices was assumed to be very small because we excluded patients with acute myocardial infarction in the present analysis. Fifth, we did not have information about the use of vascular suturing devices. Sixth, because the CREDO-Kyoto PCI Registry Cohort-2 was not designed to investigate the performance of ARC HBR criteria, data were not available for some ARC HBR criteria. Therefore, the prevalence of HBR patients would have been underestimated in the present study. Seventh, we defined major bleeding as GUSTO moderate/severe bleeding, whereas major bleeding is defined as Bleeding Academic Research Consortium (BARC) Type 3 or 5 in the ARC HBR initiative. However, the rates of major bleeding, defined as either GUSTO moderate/severe or BARC Type 3 or 5, were reported to be comparable in several previous studies.^{32,33} Finally, we could not investigate the minor puncture site bleeding that did not cause hemodynamic instability or require transfusion, because GUSTO moderate/severe

bleeding was defined as a bleeding event in the registry.

In conclusion, compared with transfemoral PCI, transradial PCI was associated with a lower risk for 30-day major bleeding and mortality in HBR patients, as defined by ARC HBR criteria, but not in non-HBR patients.

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Conflict of Interest

The CREDO-Kyoto PCI/CABG Registry Cohort-2 was supported by Pharmaceuticals and Medical Devices Agency in Tokyo, Japan. T. Kimura has served on the advisory board of Abbott Vascular. All other authors have no relationships relevant to the contents of this paper to disclose.

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Supplementary Files

Please find supplementary file(s);
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