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ORIGINAL RESEARCH

Association Between Radial Versus Femoral Access for Percutaneous Coronary Intervention and Long-Term Mortality

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BACKGROUND: Percutaneous coronary intervention with radial arterial access has been associated with fewer occurrences of major bleeding. However, published data on the long-term mortality and major adverse cardiac events after percutaneous coronary intervention with radial or femoral arterial access are inconclusive.

METHOD AND RESULTS: This was a territory-wide retrospective cohort study including 26 022 patients who underwent first-ever percutaneous coronary intervention between January 1, 2010 and December 31, 2017 in Hong Kong. Among the 14 614 patients matched by propensity score (7307 patients in each group), 558 (7.6%) and 787 (10.8%) patients died during the observation period in the radial group and femoral group, respectively, resulting in annualized all-cause mortality rates of 2.69% and 3.87%, respectively. The radial group had a lower risk of all-cause mortality compared with the femoral group up to 3 years after percutaneous coronary intervention (hazard ratio [HR], 0.70; 95% CI, 0.63–0.78; $P<0.001$). Radial access was associated with a lower risk of major adverse cardiac events (HR, 0.78; 95% CI, 0.73–0.83, $P<0.001$), myocardial infarction after hospital discharge (HR, 0.78; 95% CI, 0.70–0.87, $P<0.001$), and unplanned revascularization (HR, 0.76; 95% CI, 0.68–0.85, $P<0.001$). The risks of stroke were similar across the 2 groups (HR, 0.96; 95% CI, 0.82–1.13, $P=0.655$).

CONCLUSIONS: Radial access was associated with a significant reduction in all-cause mortality at 3 years compared with femoral access. Radial access was associated with reduced risks of myocardial infarction and unplanned revascularization, but not stroke. The benefits were sustained beyond the early postoperative period.

Key Words: mortality ■ percutaneous coronary intervention ■ radial artery catheter

In patients with coronary artery disease undergoing percutaneous coronary interventions (PCI), use of radial arterial access has been consistently shown to reduce major bleeding at the access site compared with femoral access in many randomized trials, especially those recruiting patients with acute coronary syndrome (ACS).[1–5] However, there are still reservations about widespread adoption of transradial PCI, and its uptake in the United States is lagging.[6–8] This may be partly contributed to by a longer learning curve, and thus requiring higher procedural volumes to achieve and maintain proficiency for transradial PCI.[7,9] Another potential barrier is that the effects of radial access on mortality and major adverse cardiac events (MACE) have been variable across randomized and observational trials.[1–5,7,10,11]

There is evidence that certain adverse events that are reduced by radial access have important prognostic implications on long-term mortality. For example, it has been demonstrated that bleeding events after PCI are associated with a 2- to 3-fold increase in long-term mortality.[12–15] Radial access has also been associated with less acute kidney injury in a substudy from the MATRIX (Minimizing Adverse Hemorrhagic Events by

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CLINICAL PERSPECTIVE

What Is New?

- The uptake of transradial percutaneous coronary intervention is variable, in part because of conflicting results with regard to cardiac outcomes.
- This is one of the largest studies that focused on the effects of arterial access during percutaneous coronary intervention on long-term cardiac outcomes.
- Use of radial access was associated with significant reduction in all-cause mortality, major adverse cardiac events, myocardial infarction, unplanned revascularization, but not stroke, at 3 years.

What Are the Clinical Implications?

- Transradial percutaneous coronary intervention could be an important strategy to improve long-term mortality and cardiac outcomes.
- A "radial first" approach during percutaneous coronary intervention should be encouraged.

Nonstandard Abbreviations and Acronyms

MACE	major adverse cardiac events

Transradial Access Site and Systemic Implementation of Angiox) randomized trial.[16,17] Taken together, the effect on such adverse events as major bleeding and acute kidney injury may translate to decreased long-term mortality using a radial access approach.[18,19]

Our current knowledge on the relationship between access site for PCI and mortality has mainly come from observation and randomized studies with short- to midterm (1-year) follow-up,[1–5,7,10,11,20] and the effects of access site on long-term mortality are largely unknown. We hypothesized that use of radial access is associated with lower long-term mortality rates compared with use of femoral access in patients undergoing PCI.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population and Design

Data from all patients who underwent first-ever PCI between January 1, 2010 and December 31, 2017 from all 14 publicly funded hospitals that offer PCI in Hong Kong were reviewed. Patients' baseline characteristics, exposures, and outcomes were retrieved from the Clinical Data and Analysis Reporting System, an electronic data repository that captures clinical parameters of all patients managed in publicly funded institutions in Hong Kong. The PCI Registry is part of the Clinical Data and Analysis Reporting System that systematically records patient and procedural characteristics related to PCI. The study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster. Requirement for informed consent was waived because of the retrospective nature of the study.

We included all adult patients (18 years of age or older) who underwent PCI with documentation of femoral or radial arterial access use. Exclusion criteria were patients who had prior history of PCI, had concurrent radial and femoral accesses defined as both radial and femoral sheaths being placed, or required any mechanical circulatory support including intra-aorta balloon pump, percutaneous ventricular assist device, or extracorporeal membrane oxygenation.

Definitions of Exposure and Outcome Variables

The use of radial versus femoral arterial access site was defined as successful placement of an arterial sheath for PCI. The primary outcome was all-cause mortality in a time-to-event analysis up to 3 years from index PCI. The secondary outcomes were a composite outcome of MACE including all-cause mortality, myocardial infarction after hospital discharge, unplanned coronary revascularization, and stroke; and the individual components of the composite outcome, in a time-to-event analysis for up to 3 years from index PCI. Details of exposure and outcome definitions are shown in Data S1.

Statistical Analysis

All analyses were performed with prespecified end points and statistical methods. We constructed a propensity score that predicted the likelihood of radial versus femoral access with variables selected a priori based on data in the published literature and biological plausibility: sex, age, ethnicity (Chinese versus non-Chinese), tobacco use, diabetes mellitus, hypertension, dyslipidemia, cerebrovascular disease, chronic obstructive pulmonary disease,[21,22] peripheral vascular disease,[23] history of malignancy,[24] cirrhosis,[25] estimated glomerular filtration rate, white blood cell count >10^9/L,[26] anemia (hemoglobin <13 g/dL for men, <12 g/dL for women),[27] atrial fibrillation or flutter, oral anticoagulant use, previous myocardial infarction, prior coronary arterial bypass grafting, previous heart failure, decompensated heart failure on presentation (New York Heart Association Class III or IV), cardiogenic

shock on presentation (but not requiring mechanical circulatory support), ventricular tachycardia before PCI,[28] PCI urgency (elective, urgent, emergency),[29,30] indication for PCI (stable angina, unstable angina, non–ST-segment–elevation myocardial infarction, ST-segment–elevation myocardial infarction [STEMI]),[29,30] number of major epicardial arteries involved,[30] proportion of radial access use by institution (in quartiles),[31] and PCI year (2010–2013 versus 2014–2017).

The study cohort consisted of 2 comparison groups—"radial group" and "femoral group"—generated by 1:1 propensity-score-matching using a caliper of 0.2 times the SD of the propensity score. Unadjusted analyses were made using χ^2 tests for categorical variables and Student *t* test or Wilcoxon rank-sum tests for continuous variables. Kaplan–Meier survival curves were constructed for study groups and compared using the log-rank test. Cox proportional hazards regression was performed to evaluate the relationship between access site and clinical outcomes. Landmark analysis was performed using the same regression model for all-cause mortality occurring between 0 to 30 days and 30 days to 3 years.

Sensitivity Analyses

We performed sensitivity analysis by including all patients before propensity score matching. A multivariable Cox proportional hazards model adjusting for the same variables in the propensity score model was used to examine the association between access site and mortality in a time-to-event analysis.

To assess any residual confounding by treatment selection, we performed falsification testing with 2 clinical outcomes: new diagnosis of cancer and new gastrointestinal bleeding after PCI.[11] They were selected based on their association with mortality but were biologically unlikely to be causally related to the choice of access site.

The complete case method was adopted to address missing data in the primary statistical analysis. To test the robustness of our results, the multivariable Cox regression analysis was repeated with the entire cohort using the technique of multiple imputations by chained equations.

Exploratory Analyses

We studied the effect modification on the relationship between access site and mortality by pre-defined clinical variables, and introduced interaction terms to the Cox regression model. We utilized the Acuity Score, which was validated to categorize the baseline bleeding risks of the patients.[32]

Data management and statistical analyses were performed with Stata software, version 16 (StataCorp LP). For the primary end point, a 2-tailed *P* value of <0.05 was considered statistically significant. For the secondary end points, Bonferroni correction was used to adjust for multiple testing, and a 2-tailed *P* value of <0.01 was considered statistically significant.

RESULTS

Patients and Characteristics

Between January 2010 and December 2017, a total of 26 022 patients were considered for inclusion: 1559 (6%) were excluded because of any of the following exclusion criteria: age younger than 18 years, access site unknown, concurrent radial and femoral accesses, or mechanical circulatory support required. Of the remaining 24 463 patients, a total of 1655 (6.7%) were excluded from the complete case analysis because of missing values in any of the variables used in the propensity score model. Characteristics of all patients (n=22 808) before propensity score matching are shown in Figures S1 and S2. The proportion of radial access increased monotonically from 33% in year 2010 to 70% in year 2017 (Figure S1).

Seven thousand three hundred seven matched pairs of patients were generated after 1:1 propensity score matching (Figure 1 in the main article and Figure S2). Table 1 shows the baseline characteristics of the study population. Patients in the radial group were less likely to have a history of cerebrovascular disease, reduced creatinine clearance, and anemia; and were more likely to have PCI done in institutions with a higher proportion of radial access use and in the more recent period. Table 2 shows the procedural and postprocedural characteristics of the study population. Of note, the radial group had a lower rate of drop in hemoglobin >2 g/dL and blood transfusion after PCI.

Primary Outcome

The primary outcome of all-cause mortality developed in 558 (7.6%) and 787 (10.8%) patients in the radial group and femoral group, respectively, with annualized mortality rates of 2.7% and 3.9%. Patients in the radial group had a lower risk of all-cause mortality compared with the femoral group up to 3 years after PCI (hazard ratio [HR], 0.70; 95% CI, 0.63–0.78; *P*<0.001), as shown in Table 3 and Figure 2. The radial group also had a lower risk of cardiovascular mortality up to 3 years (HR, 0.67; 95% CI, 0.57–0.79; *P*<0.001). Between 0 and 30 days, all-cause mortality occurred in 93 (1.3%) and 146 (2.0%) patients in the radial and femoral group, respectively (HR, 0.63; 95% CI, 0.49–0.82; *P*=0.001). Between 30 days and 3 years, all-cause mortality occurred in 465 (annualized risk 2.3%) and 641 (annualized risk 3.2%) patients in the radial and femoral group, respectively (HR, 0.71; 95% CI, 0.63–0.80; *P*<0.001).

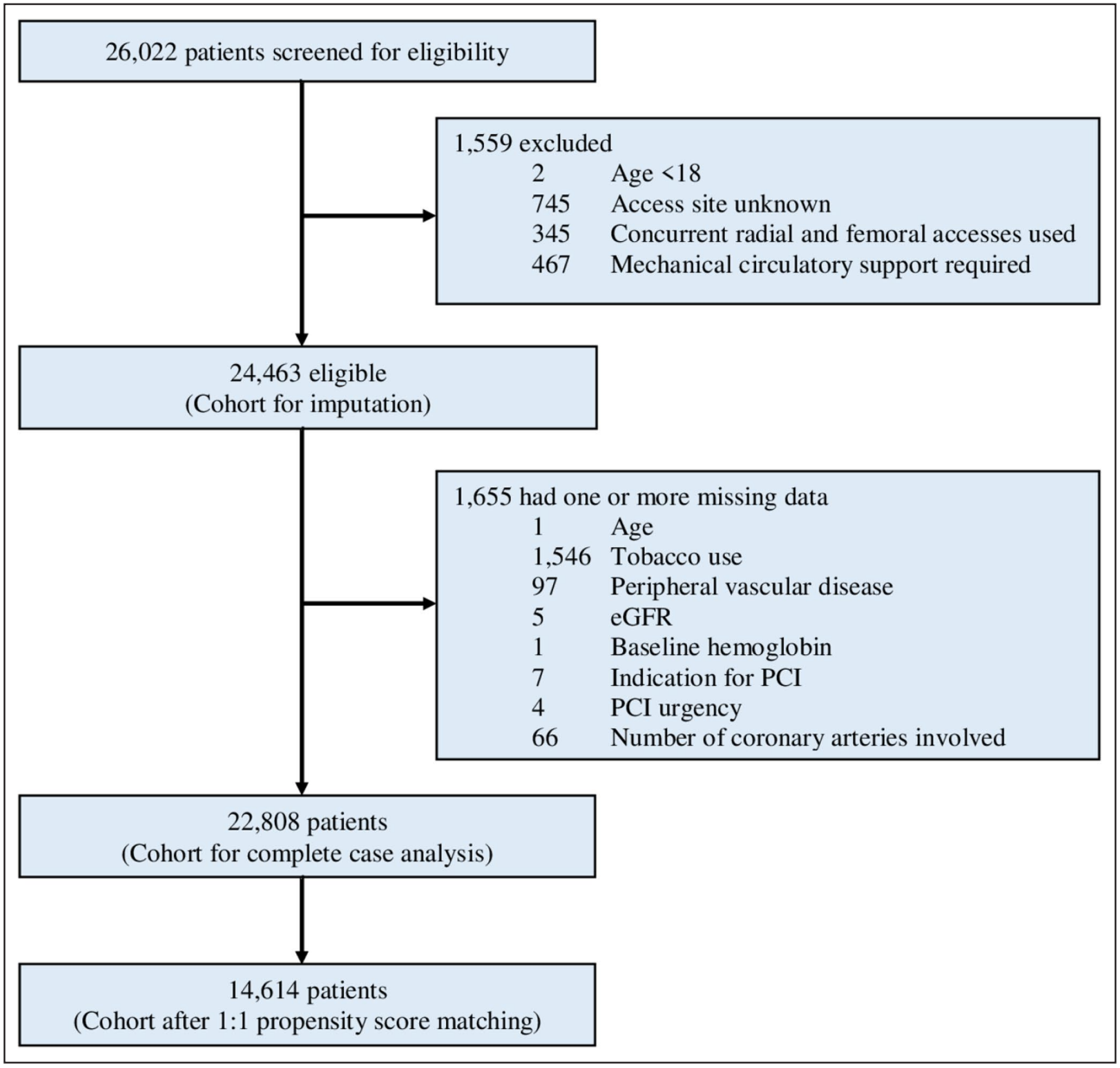

Figure 1. Study profile.
eGFR indicates estimated glomerular filtration rate; and PCI, percutaneous coronary intervention.

Secondary Outcomes

Radial access was associated with lower risks of MACE (HR, 0.78; 95% CI, 0.73–0.83; *P*<0.001), myocardial infarction after hospital discharge (HR, 0.78; 95% CI, 0.70–0.87; *P*<0.001), and unplanned revascularization (HR, 0.76; 95% CI, 0.68–0.85; *P*<0.001). The risks of stroke were similar across the 2 groups (HR, 0.96; 95% CI, 0.82–1.13; *P*=0.655). These results are shown in Table 3 and Figure 3A through 3D.

Sensitivity Analyses

We analyzed the outcomes of all 22 808 patients with complete information before propensity score matching. All-cause mortality occurred in 872 and 1256 patients in the radial and femoral group, respectively, corresponding to an annual risk of 2.39% and 4.57%, respectively (unadjusted HR, 0.52; 95% CI, 0.48–0.57; *P*<0.001). In the multivariable Cox regression model adjusting for all previously mentioned variables, the risk of all-cause mortality remained lower in the radial group compared with the femoral group (HR, 0.67; 95% CI, 0.61–0.73; *P*<0.001).

Falsification testing showed that the risks of cancer diagnosed after PCI (HR, 0.87; 95% CI, 0.7–1.05; *P*=0.148) and gastrointestinal bleeding (HR, 0.79; 95% CI, 0.54–1.14; *P*=0.207) were not significantly different between the radial and femoral groups.

Table 1. Baseline Characteristics of Patients After Propensity Score Matching

Characteristic	Radial Group N=7307	Femoral Group N=7307	*P* Value	Standardized Difference
Female, n (%)	1681 (23.0%)	1740 (23.8%)	0.249	0.019
Age, y, mean (SD)	64.6 (11.3)	64.8 (11.8)	0.257	0.019
Chinese, n (%)	6924 (94.8%)	6903 (94.5%)	0.442	−0.013
Tobacco use, n (%)	3400 (46.5%)	3352 (45.9%)	0.426	−0.013
Diabetes mellitus, n (%)	2509 (34.3%)	2569 (35.2%)	0.297	0.017
Hypertension, n (%)	4635 (63.4%)	4692 (64.2%)	0.326	0.016
Dyslipidemia, n (%)	4614 (63.1%)	4602 (63.0%)	0.837	−0.003
Cerebrovascular disease, n (%)	668 (9.1%)	741 (10.1%)	0.041	0.034
Chronic obstructive pulmonary disease, n (%)	169 (2.3%)	186 (2.5%)	0.361	0.015
Peripheral vascular disease, n (%)	88 (1.2%)	100 (1.4%)	0.378	0.015
History of malignancy, n (%)	369 (5.0%)	385 (5.3%)	0.550	0.010
Cirrhosis, n (%)	21 (0.3%)	19 (0.3%)	0.752	−0.005
eGFR, mL/min per 1.73 m^2, mean (SD)	82.8 (25.3)	81.3 (30.0)	0.002	−0.051
eGFR <50 mL/min per 1.73 m^2, n (%)	646 (8.8%)	907 (12.4%)	<0.001	0.116
White blood cell count, 10^9/L, mean (SD)	8.2 (2.9)	8.2 (3.0)	0.653	0.007
Anemia, n (%)	2173 (29.7%)	2414 (31.7%)	0.011	0.042
Atrial fibrillation or flutter, n (%)	380 (5.2%)	401 (5.5%)	0.440	0.013
On anticoagulant before PCI, n (%)	182 (2.5%)	194 (2.7%)	0.531	0.010
Previous myocardial infarction, n (%)	880 (12.0%)	907 (12.4%)	0.495	0.011
Previous coronary artery bypass surgery, n (%)	48 (0.6%)	42 (0.6%)	0.526	−0.011
Previous heart failure, n (%)	546 (7.5%)	588 (8.0%)	0.194	0.021
NYHA class III–IV in last 2 wk before PCI, n (%)	286 (3.9%)	297 (4.1%)	0.642	0.008
Cardiogenic shock, n (%)	136 (1.9%)	126 (1.7%)	0.533	−0.010
Ventricular tachycardia in <48 h before PCI, n (%)	156 (2.1%)	157 (2.1%)	0.954	0.001
PCI urgency, n (%)			0.231	0.028
Elective	4276 (58.5%)	4209 (57.6%)		
Urgent	2156 (29.5%)	2157 (29.5%)		
Emergent	893 (12.2%)	972 (13.3%)		
Indication for PCI, n (%)			0.254	0.033
Stable angina	1413 (19.3%)	1373 (18.8%)		
Unstable angina	1534 (21.0%)	1523 (20.8%)		
Non–ST-segment–elevation myocardial infarction	3467 (47.4%)	3439 (47.1%)		
ST-segment–elevation myocardial infarction	893 (12.2%)	972 (13.3%)		
Number of major epicardial artery involved, n (%)			0.710	0.014
One-vessel disease	3336 (45.7%)	3295 (45.1%)		
Two-vessel disease	2465 (33.7%)	2470 (33.8%)		
Three-vessel disease	1506 (20.6%)	1542 (21.1%)		
Proportion of radial access use by institution, n (%)			<0.001	−0.165
First quantile (lowest radial use)	2787 (38.1%)	3205 (43.9%)		
Second quantile	2019 (27.6%)	2069 (28.3%)		
Third quantile	1009 (13.8%)	987 (13.5%)		
Fourth quantile (highest radial use)	1492 (20.4%)	1046 (14.3%)		
Year of PCI, n (%)			<0.001	−0.073
2010–2013	2796 (38.3%)	3058 (41.9%)		
2014–2017	4511 (61.7%)	4249 (58.1%)		

Note: Comparison by Pearson χ^2 test for categorical data and by Student *t* tests for continuous data. eGFR indicates glomerular filtration rate; NYHA, New York Heart Association; and PCI, percutaneous coronary intervention.

Table 2. Procedural and Postprocedural Characteristics of Patients

Characteristic	Radial Group N=7307	Femoral Group N=7307	*P* Value	Standardized Difference
Intravascular imaging, n (%)	4211 (57.6%)	3151 (43.1%)	<0.001	−0.293
Intravascular ultrasonography, n (%)	2909 (39.8%)	2414 (33.0%)	<0.001	−0.141
Optic coherence tomography, n (%)	1374 (18.8%)	760 (10.4%)	<0.001	−0.240
Contrast volume in mL, median (IQR)	135 (95–190)	150 (100–200)	<0.001	0.097
Angiographic success, n (%)	7167 (98.1%)	7041 (96.5%)	<0.001	−0.099
Drop in hemoglobin >2 g/dL, n (%)	1172 (16.0%)	1295 (17.9%)	0.007	0.045
Days until hemoglobin nadir, median (IQR)	1 (0–1)	1 (0–3)	<0.001	0.061
Blood transfusion after PCI	113 (1.5%)	267 (3.7%)	<0.001	0.133
Packs of blood transfused, median (IQR)	2 (1–3)	2 (1–2)	0.274	−0.043
Vascular complication requiring surgery	4 (0.1%)	5 (0.1%)	0.737	0.005
Anemia after PCI, n (%)	2715 (41.2%)	3109 (46.1%)	<0.001	0.099
Acute kidney injury*	1205 (16.5%)	1509 (20.7%)	<0.001	0.107
Gastrointestinal bleeding within 30 d, n (%)	35 (0.5%)	37 (0.5%)	0.813	0.004
Upper endoscopy within 30 d, n (%)	50 (0.7%)	63 (0.9%)	0.220	0.020
Aspirin on discharge, n (%)	7122 (97.5%)	3137 (97.7%)	0.420	0.013
P2Y12 inhibitor on discharge, n (%)	7198 (98.5%)	7194 (98.5%)	0.787	−0.004
Potent P2Y12 inhibitor on discharge, n (%)	1309 (17.9%)	946 (12.9%)	<0.001	−0.138
Proton pump inhibitor on discharge, n (%)	4453 (60.9%)	4335 (59.3%)	0.046	−0.033
P2Y12 inhibitor duration, median (IQR) in d	365 (364–403)	365 (352–411)	0.048	−0.015
Statin on discharge, n (%)	6999 (95.8%)	6945 (95.0%)	0.033	−0.035
ACE inhibitor or ARB on discharge, n (%)	4933 (67.5%)	5076 (69.5%)	0.011	0.059
β-blocker on discharge, n (%)	5242 (71.7%)	5459 (74.7%)	<0.001	0.067
Anticoagulant on discharge, n (%)	266 (3.6%)	262 (3.6%)	0.859	−0.003

Note: Comparison by Pearson χ^2 test for categorical data and by Wilcoxon rank-sum tests for continuous data. ACE indicates angiotensin converting enzyme; ARB, angiotensin receptor blocker; IQR, interquartile range; and PCI, percutaneous coronary intervention.

*Rise in creatinine >1 mg/dL or >50% from baseline within 7 days of PCI.

A total of 8 variables in the propensity score matching model had missing data. Tobacco use, the variable that had the largest amount of missing data, had 1546 (6.3%) missing values. Multiple imputation was conducted, and the imputed cohort included all 1655 (6.7%) patients who were excluded because of missing values in any of the variables used in the model. The association between radial access and all-cause mortality from the imputed data set remained consistent with the complete case cohort (HR, 0.65; 95% CI, 0.59–0.71; *P*<0.001).

Exploratory Analyses

We explored effect modification of the access site–mortality association by various patient and procedural parameters (Table 4 and Figure 4). There were significantly greater benefits attributable to radial access in PCI that were performed in 2014 to 2017 compared with 2010 to 2013 (*P* for interaction=0.024), in institutions with higher use of radial access (*P* for interaction=0.002), and in patients with higher predicted bleeding risk by Acuity Score (*P* for interaction=0.041).

DISCUSSION

In this cohort of 14 614 propensity score matched adult patients undergoing first-ever PCI, we showed that radial arterial access was associated with a reduction in risk of all-cause mortality within 3 years of the procedure compared with femoral arterial access, adding to previous knowledge about benefits of radial access on shorter-term mortality and bleeding complications. The access site–mortality association remained consistent after adjustment for factors potentially affecting the choice of access site and multiple sensitivity analyses. Specifically, radial access was associated with lower adjusted risks of MACE, myocardial infarction after discharge, and unplanned coronary revascularization, but similar risks of strokes.

Radial access has been consistently shown to reduce major bleeding at access site in several randomized trials representing a wide range of clinical syndromes.[1–5] However, its effects on mortality and MACE are less conclusive and further limited by a follow-up period of no more than 1 year. In the MATRIX trial and RIVAL (Radial Versus Femoral Access for

Table 3. Primary and Secondary Outcomes Stratified by Study Groups

Outcomes	Annualized Rate		Hazard Ratio	95% CI	*P* Value
	Radial Group	Femoral Group			
Primary					
All-cause mortality	2.69%	3.87%	0.70	0.63–0.78	<0.001
Cardiovascular mortality	1.13%	1.70%	0.67	0.57–0.79	<0.001
Secondary					
Major adverse cardiac events	8.19%	10.60%	0.78	0.73–0.83	<0.001
Myocardial infarction	3.10%	4.00%	0.78	0.70–0.87	<0.001
Unplanned revascularization	2.61%	3.46%	0.76	0.68–0.85	<0.001
Stroke	1.52%	1.58%	0.96	0.82–1.13	0.655

Comparison by Cox proportional hazards regression.

Coronary Intervention) trials, no benefits in mortality or MACE were shown for radial access.[1,2] In contrast, in the RIFLE-STEACS (Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome) trial, which exclusively focused in patients with STEMI, a mortality benefit at 30 days was shown.[3] In a meta-analysis of 24 randomized trials, all-cause mortality was reduced with radial access only for patients with STEMI, and the follow-up period was limited to either in-hospital or 30 days.[5] Since randomized studies have strict inclusion criteria and require operators to be competent in both access options, it is imperative to confirm the findings in real-world populations. A registry of 44 804 patients found a mortality benefit with radial access for patients with STEMI.[33] Similarly, in a meta-analysis inclusive of 17 cohort studies for ACS (14 for STEMI exclusively), radial access was associated with short-term mortality benefit.[20] However, no mortality benefit was observed in several large cohort studies unrestricted on clinical

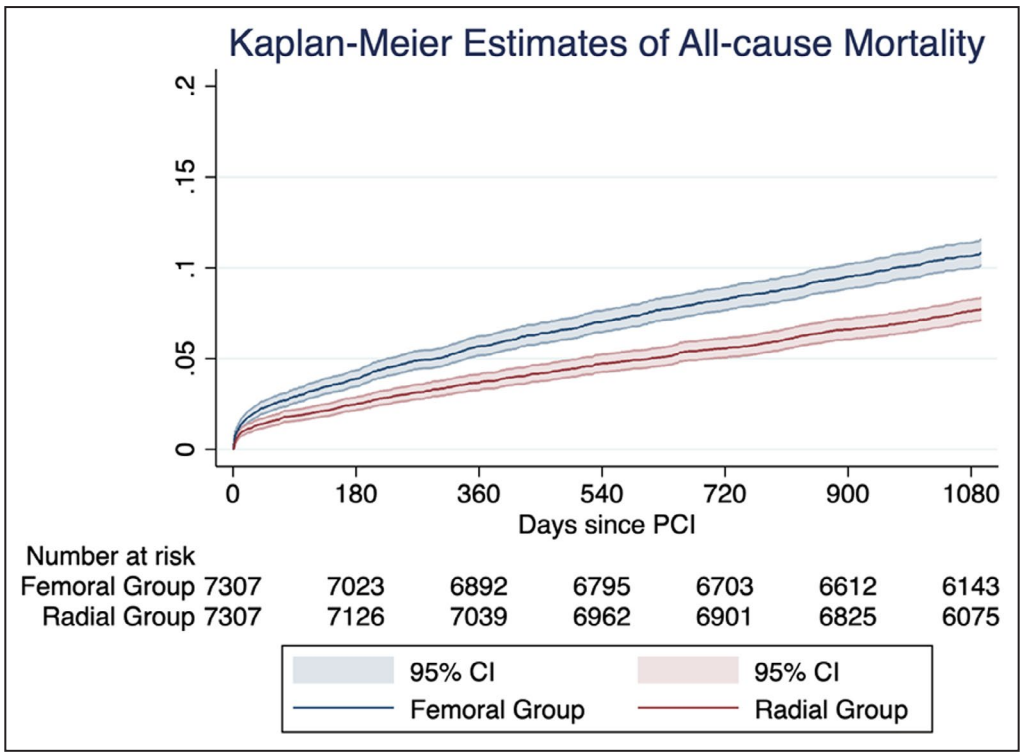

Figure 2. Primary outcome; estimated probabilities of all-cause mortality stratified by access site.
All-cause mortality at 3 years developed in 558 (7.6%) and 787 (10.8%) patients in the radial and femoral group, respectively. Patients in the radial group had a lower risk of all-cause mortality compared with the femoral group (hazard ratio, 0.70; 95% CI, 0.63–0.78; *P*<0.001). PCI indicates percutaneous coronary intervention.

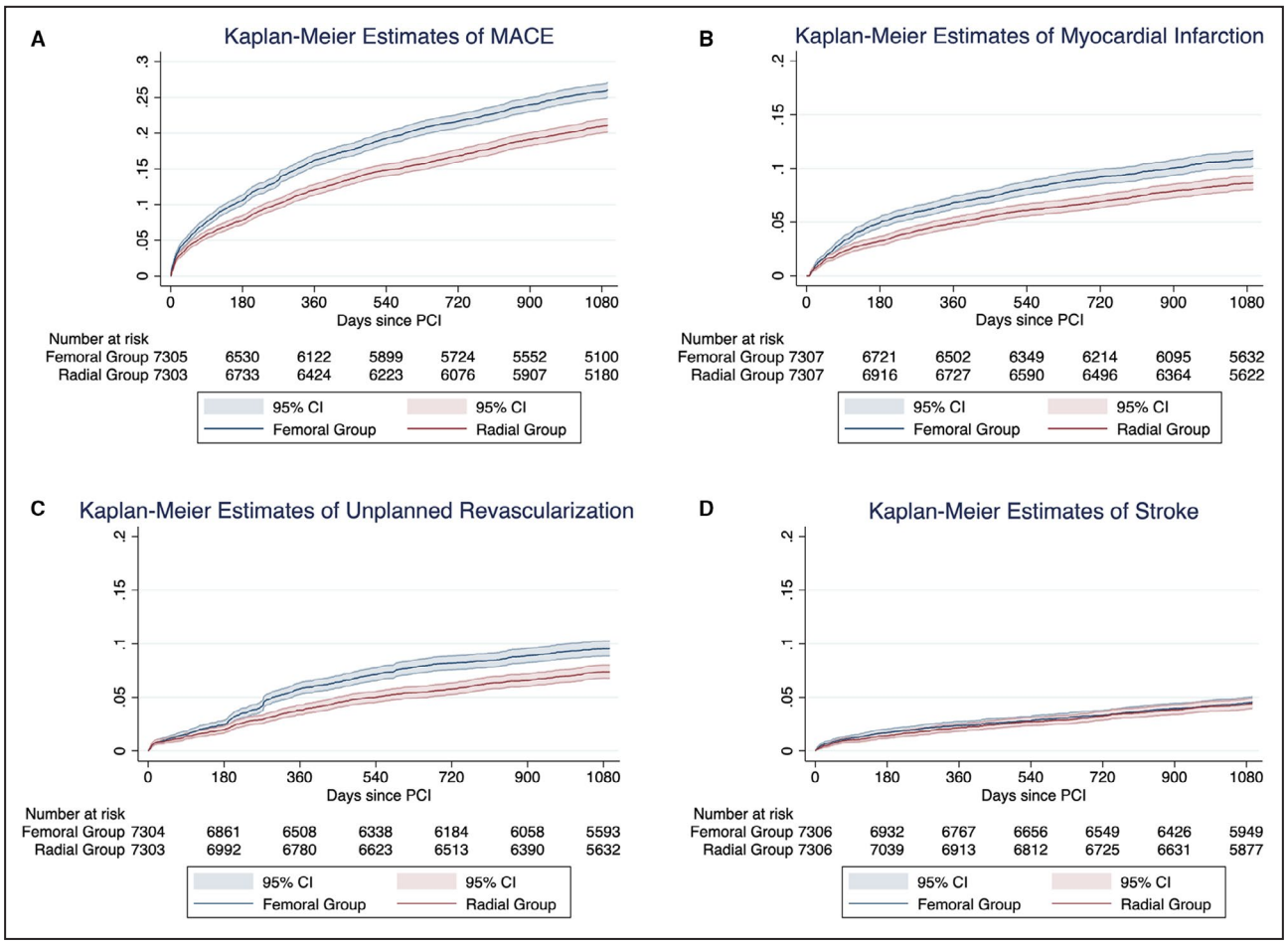

Figure 3. Secondary outcomes; radial access was associated with lower risks of major adverse cardiac events, myocardial infarction after hospital discharge, and unplanned revascularization but similar risks of stroke.
A, Secondary outcome: Estimated probabilities of MACE stratified by access site. Patients in the radial group had a lower risk of MACE compared with the femoral group (hazard ratio, 0.78; 95% CI, 0.73–0.83; *P*<0.001). **B**, Secondary outcome: Estimated probabilities of myocardial infarction after hospital discharge stratified by access site. Patients in the radial group had a lower risk of myocardial infarction after hospital discharge compared with the femoral group (hazard ratio, 0.78; 95% CI, 0.70–0.87; *P*<0.001). **C**, Secondary outcome: Estimated probabilities of unplanned revascularization stratified by access site. Patients in the radial group had a lower risk of unplanned revascularization compared with the femoral group (hazard ratio, 0.76; 95% CI, 0.68–0.85; *P*<0.001). **D**, Secondary outcome: Estimated probabilities of stroke stratified by access site. Patients in the radial group had a similar risk of stroke compared with the femoral group (hazard ratio, 0.96; 95% CI, 0.82–1.13; *P*=0.655). MACE indicates major adverse cardiac events; and PCI, percutaneous coronary intervention.

presentations,[34–36] or restricted to non–ST-segment–elevation myocardial infarction.[37] To the best of our knowledge, these are the first real-world data showing a mortality benefit from radial access across a diverse population; the benefit was seen at 30 days, and further accrued for up to 3 years.

One plausible mechanism for the long-term effect on mortality is through the reduction in post-PCI bleeding events, blood transfusions, and major vascular complications in using radial artery access. These complications, such as femoral bleeding and blood transfusion, have been associated with increased mortality up to 6 years after PCI.[38] In a substudy of the HORIZONS-AMI (The Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial, patients with post-PCI bleeding during an in-hospital stay were associated with 4-fold risks of mortality at 3 years with consistent associations across different landmark analyses; and the excess risks of late mortality from post-PCI bleeding continued to monotonically accrue over time.[39] In agreement with these findings, our data showed that radial access was associated with less frequent drop in hemoglobin and anemia after PCI, less transfusion after PCI, but similar rates of vascular complication requiring surgery, gastrointestinal bleeding, and upper endoscopy within 30 days, suggesting that radial access was associated with lower rates of clinical bleeding such as groin and retroperitoneal hematoma that did not necessitate major surgery. Not surprisingly, we also found that the

Table 4. Subgroup Analysis Examining Differential Effects of Access Site on the Primary Outcome

Subgroup	Hazard Ratio	95% CI	*P* Value for Interaction
All patients	0.70	0.63–0.78	
Sex			0.363
Male	0.68	0.60–0.77	
Female	0.76	0.62–0.93	
Age group			0.224
Age <65 y	0.62	0.50–0.77	
Age >65 y	0.72	0.64–0.82	
Diabetes mellitus			0.777
No diabetes mellitus	0.71	0.61–0.83	
With diabetes mellitus	0.69	0.59–0.80	
Previous CABG			0.228
No previous CABG	0.69	0.62–0.77	
Previous CABG	1.24	0.47–3.27	
Baseline renal function			0.195
eGFR >50 mL/min per 1.73 m^2	0.81	0.70–0.92	
eGFR <50 mL/min per 1.73 m^2	0.69	0.58–0.83	
Indication for PCI			0.266
Stable coronary artery disease	0.82	0.60–1.12	
Acute coronary syndrome	0.68	0.61–0.77	
Primary PCI			0.325
Nonprimary PCI	0.68	0.61–0.77	
Primary PCI	0.79	0.61–1.02	
Cardiogenic shock*			0.067
No cardiogenic shock	0.71	0.63–0.79	
Cardiogenic shock	0.47	0.29–0.76	
PCI date			0.024
2010–2013	0.82	0.68–0.99	
2014–2017	0.63	0.55–0.72	
Radial use by institution			0.002
Low use	0.78	0.68–0.89	
High use	0.55	0.46–0.65	
Radial use by institution and year			0.029
Low use	0.82	0.65–1.05	
High use	0.58	0.47–0.71	
Predicted bleeding risk			0.041
Low risk	0.85	0.69–1.06	
High risk	0.66	0.58–0.75	

Comparison by Cox proportional hazards regression. CABG indicates coronary artery bypass surgery; eGFR, glomerular filtration rate; and PCI, percutaneous coronary intervention.

*Cardiogenic shock without mechanical circulatory support.

mortality benefit of radial access was different in patients depending on the Acuity Score; patients with greater risks of bleeding benefited more from radial access. Another known benefit of radial access was lower volumes of radiographic contrast use,[40] and lower rates of acute kidney injury after PCI.[16,41] This was also observed in our cohort. Since acute kidney injury after PCI is associated with increased long-term mortality,[18,19] this may be another mechanism underlying the effect of radial access on survival. Finally, potent P2Y12 inhibitors have been shown to improve survivals after PCI in patients with ACS.[42] The reduction in bleeding risk by radial access may have facilitated the more liberal use of potent P2Y12 inhibitors, hence explaining the continuing accrual of survival benefit beyond the early post-PCI phase.

In our secondary analysis, myocardial infarction and unplanned coronary revascularization were less frequent in the transradial group. This may be attributed to the reported association between post-PCI bleeding and subsequent myocardial infarction.[12,43] Post-PCI bleeding and blood transfusion lead to a proinflammatory state, platelet aggregation, and activation of coagulation cascade, increasing the risk of thrombotic events.[44–46] Interruption of therapies including dual antiplatelet and/or antithrombotic therapy after bleeding complications also results in more ischemic events.[47,48] Furthermore, less access site bleeding during the PCI procedure may enable operators to focus their attention on optimization of results (eg, by the use of intravascular imaging), which may result in better long-term outcomes.[49] In our data, intravascular imaging was more frequently used in the radial group, although this should be interpreted with caution as it may be confounded by operators' expertise and preference.

The current European Society of Cardiology guidelines have a class I, level of evidence A, recommendation for use of radial access for PCI in patients with ACS.[50] The American Heart Association also supports a "radial first" strategy for patients with ACS.[7] Our data support these recommendations and invite future randomized trials to evaluate the mortality benefit in patients with stable coronary artery disease. Moreover, we observed that radial access was more beneficial when institutions or operators had accumulated more experience and procedural volumes, which was consistent with the known learning curve required to optimize outcomes.[9] We also observed that the mortality benefits of radial access were more pronounced in recent years, which paralleled a growing portion of transradial PCI. However, such mortality benefit was also significant in hospitals and time periods with less radial experience.

This study had several strengths. First, it captured representative territory-wide data with robust long-term outcomes and minimal loss to follow-up, because nearly all patients continued to receive care under the same healthcare system. Second, unlike in randomized trials, which are conducted in highly selected

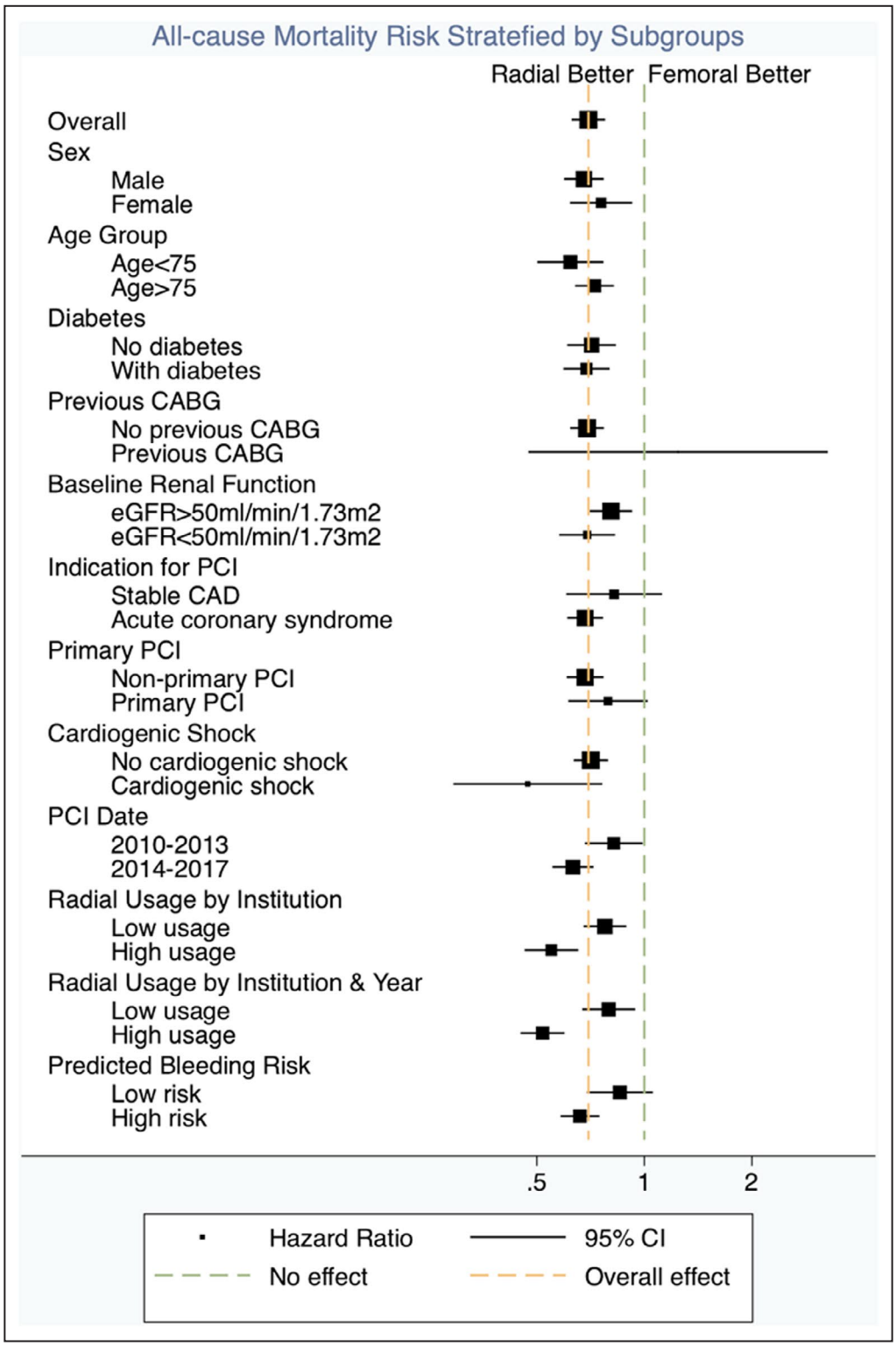

Figure 4. Subgroup analysis.
Effect modification was significant across PCI date, radial use by institution alone and by institution-year, and predicted bleeding risk. CABG indicates coronary artery bypass surgery; CAD, coronary artery disease; and PCI, percutaneous coronary intervention.

centers competent in both transradial and transfemoral PCI, we showed that the mortality benefit of radial access was appreciable even in real-world settings with no restriction with regard to clinical scenarios, institutions, and operators. Third, our data were retrieved from a population-based electronic database with

comprehensive information on vascular access and subsequent events recorded a priori, thus minimizing the selection, information, and recall biases. Fourth, this was a territory-wide study with a large sample size, enabling us to control for many potential confounders. The results were also consistent across primary, secondary, and sensitivity analysis.

This study had some limitations. First, the observational nature of the study conferred risks of unmeasured confounding and bias, but we had adjusted extensively by propensity score matching for potential confounders that may affect the choice of access site and outcomes, and the findings were consistent in many sensitivity analyses. In falsification analysis, the absence of exposure effect on risks of cancer and gastrointestinal bleeding suggests minimal residual confounding. Nonetheless, differences in use of intravascular imaging and patterns of medication prescription after discharge could potentially represent intermediate mechanisms of the association under study. Second, adjustment was made for choice of access site at institutional but not individual operator's level; hence, the study results may only be applicable to operators with levels of technical proficiency similar to operators in this study. Nevertheless, we used individual institution and time period as surrogates, and found that the benefit of radial access was still significant across different levels of radial experience albeit for a different magnitude. Third, the radial paradox, where benefits conferred by transradial PCI are accompanied by a paradoxical increase in vascular complications driven by complications in transfemoral PCI, could potentially exaggerate the benefits of radial access.[51] Fourth, this study predominantly included patients of Asian descent and may not be generalizable across all PCI patients.

In conclusion, we showed that use of radial access in PCI was associated with a significant reduction in all-cause mortality at 3 years after PCI. Radial access was associated with reduced risks of MI and unplanned revascularization, but not stroke. Our findings suggest that the benefits of radial access extend beyond the early postoperative period.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Data S1
Tables S1–S2
Figures S1–S2

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Supplemental Material

Data S1.

ENDPOINT DEFINITIONS

Death

Deaths is classified as cardiovascular or non-cardiovascular. The cause of death will be determined by the principal condition that resulted in the death, not the immediate mode of death. Managing physicians will utilize all available information provided, along with clinical expertise, in their adjudication of the cause of death.

Cardiovascular death

Death due to cardiovascular causes. They include:

- death from acute myocardial infarction and its complications (e.g., arrhythmia, sudden arrest, heart failure)
- sudden cardiac death
- death from heart failure
- death from stroke
- death caused by complications of cardiovascular procedures
- death from cardiovascular hemorrhage (e.g., intracranial hemorrhage, non-procedural or non-traumatic vascular rupture (e.g., aortic aneurysm), or hemorrhage causing cardiac tamponade)
- death from other cardiovascular causes not included in the above categories but with a specific, known cardiovascular cause (e.g., pulmonary embolus or peripheral arterial disease)

Myocardial Infarction after hospital discharge

Any new diagnosis coding from the table below after hospital discharge for index PCI.

410	**Acute Myocardial Infarction**
410.0	Acute myocardial infarction, of anterolateral wall
410.1	Acute myocardial infarction, of other anterior wall
410.2	Acute myocardial infarction, of inferolateral wall
410.3	Acute myocardial infarction, of inferoposterior wall
410.4	Acute myocardial infarction, of other inferior wall
410.5	Acute myocardial infarction, of other lateral wall
410.6	Acute myocardial infarction, true posterior wall infarction
410.7	Acute myocardial infarction, subendocardial infarction
410.8	Acute myocardial infarction, of other specified sites

410.9	Acute myocardial infarction, unspecified sites
410 (0)	Acute myocardial infarction
410 (1)	Myocardial infarction
411	**Other Acute and Subacute forms of Ischemic Heart Disease**
411.0	Post myocardial infarction syndrome
411.1	Intermediate coronary syndrome
411.8	Other acute and subacute forms of ischemic heart disease
411 (0)	Other acute and subacute forms of ischemic heart disease

Stroke

Any new diagnosis coding from the table below after PCI.

430	**Subarachnoid Haemorrhage, Non-traumatic**
430 (0)	Subarachnoid haemorrhage, non-traumatic
430 (1)	Rupture arteriovenous malformation in brain
430 (2)	Subarachnoid haemorrhage, due to rupture aneurysm
430 (3)	Subarachnoid haemorrhage, nontraumatic
430 (4)	Subarachnoid haemorrhage, due to ruptured mycotic aneurysm, non-traumatic
430 (5)	Subarachnoid haemorrhage – spinal, non-traumatic
430 (6)	Subarachnoid haemorrhage
430 (7)	Subarachnoid haemorrhage from carotid siphon and bifurcation
430 (8)	Subarachnoid haemorrhage from middle cerebral artery
430 (9)	Subarachnoid haemorrhage from anterior communicating artery
430 (10)	Subarachnoid haemorrhage from posterior communicating artery
430 (11)	Subarachnoid haemorrhage from basilar artery
430 (12)	Subarachnoid haemorrhage from vertebral artery
430 (13)	Subarachnoid haemorrhage intracranial artery
430 (14)	Berry aneurysm
430 (15)	Haemorrhage due to ruptured congenital cerebral aneurysm
431	**Intracerebral Haemorrhage, Non-traumatic**
431 (0)	Intracerebral haemorrhage, non-traumatic
431 (1)	Spontaneous intracerebral haemorrhage
431 (2)	Intracerebral haemorrhage, nontraumatic
431 (3)	Intracerebral haemorrhage – basilar, non-traumatic
431 (4)	Intracerebral haemorrhage – cerebellar, non-traumatic
431 (5)	Intracerebral haemorrhage – capsular, non-traumatic
431 (6)	Intracerebral haemorrhage – pontine, non-traumatic
431 (7)	Intracerebral haemorrhage – intra-ventricular, non-traumatic
431 (8)	Haemorrhagic conversion of cerebral infarction
431 (9)	Intracerebral haemorrhage

431 (10)	Intracerebral haemorrhage in hemisphere, cortical
431 (11)	Bullbar haemorrhage
431 (12)	Intracerebral haemorrhage, multiple localized
431 (13)	Cerebral haemorrhage
431 (14)	Intracerebral haemorrhage in brain stem
431 (15)	Basalis haemorrhage
431 (16)	Ventricular haemorrhage of brain
431 (17)	Intracerebral subcortical haemorrhage in hemisphere
432.1	**Subdural Hemorrhage, Non-traumatic**
433	**Occlusion and Stenosis of Percerebral Arteries**
433.0	Occlusion and stenosis of basilar artery, w/o mention of cerebral infarction
433.1	Occlusion and stenosis of carotid artery
433.2	Occlusion and stenosis of vertebral artery
433.3	Occlusion and stenosis of multiple and bilateralprecerebral, arteries
433.8	Occlusion and stenosis of other specified precerebral artery
433.9	Occlusion and stenosis of unspecified precerebral artery
433 (0)	Occlusion and stenosis of precerebral arteries
434	**Occlusion of Cerebral Arteries**
434.0	Cerebral thrombosis
434.1	Cerebral embolism
434.9	Cerebral artery occlusion, unspecified
434 (0)	Occlusion of cerebral arteries
435	**Transient Cerebral Ischemia**
435.0	Basilar artery syndrome
435.1	Vertebral artery syndrome
435.2	Subclavian steal syndrome
435.8	Other specified transient cerebral ischemias
435.9	Unspecified transient cerebral ischemia
435 (0)	Transient cerebral ischemia
436	**Acute, But Ill-defined Cerebrovascular Disease**
436 (0)	Acute cerebrovascular disease
436 (1)	Brain stem stroke syndrome
436 (2)	Cerebellar stroke syndrome
436 (3)	Stroke
436 (4)	Extension of cerebrovascular accident
436 (5)	Cerebrovascular accident

436 (6)	Ischaemic stroke

Unplanned Coronary Revascularization

Percutaneous coronary intervention (PCI) is defined as the placement of an angioplasty guidewire, balloon, or other device (eg, stent, atherectomy, brachytherapy, or thrombectomy catheter) into a native coronary artery or bypass graft for the purpose of mechanical coronary revascularization. The diagnostic assessment of coronary lesion severity by intravascular ultrasonography, coronary flow reserve, or fractional flow reserve is not considered a PCI procedure.

Coronary artery bypass grafting (CABG) is defined as a procedure performed to bypass partially or completely occluded coronary arteries with veins and/or arteries harvested from elsewhere in the body, thereby improving the blood supply to the coronary circulation supplying the myocardium.

Unplanned coronary revascularization is defined as any PCI or CABG performed not as a part of planned procedure upon the conclusion of index PCI.

BASELINE VARIABLES DEFINITIONS

Anemia

Anemia is defined as hemoglobin <13g/dL for men and hemoglobin <12g/dL for women.

PCI urgency

- Elective: Patient cardiac status has been stable in the days or weeks before the operation. The procedure can be deferred without increased risk of compromised cardiac outcome.

- Urgent: Procedure required during the same hospitalization to minimize chances of clinical deterioration or adverse outcome. Clinical conditions include (but are not limited to) acute or worsening chest pain, acute or worsening HF, acute MI, critical coronary stenosis, IABP support, UA with intravenous nitroglycerin, and rest angina.

- Emergency: Procedure required because of ongoing, refractory (difficult, complicated, and/or unmanageable), unrelenting cardiac compromise, with or without hemodynamic instability, and not responsive to any form of therapy except PCI.

Figure S1. Proportion of Radial Use by Year.

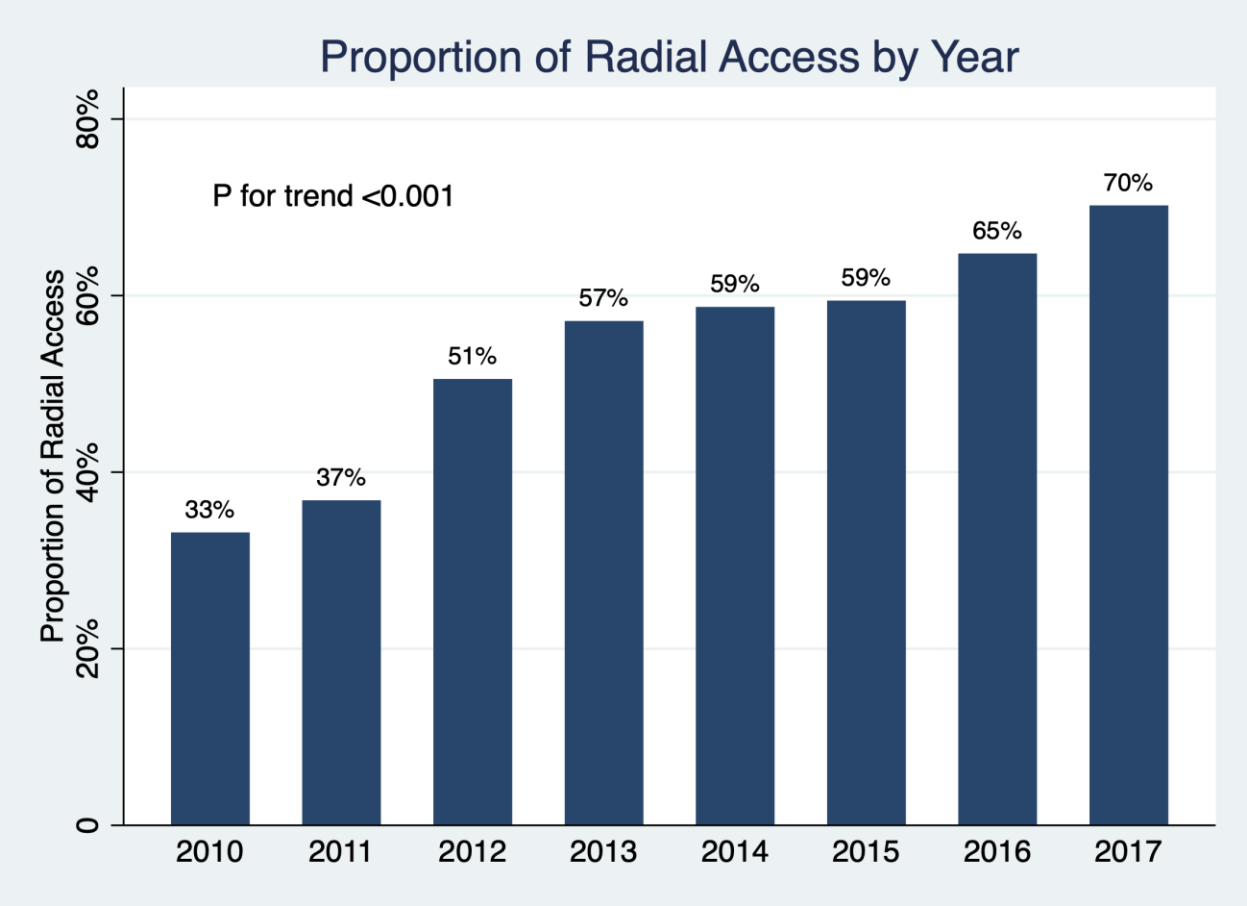

Figure S2. Propensity score distribution in the propensity score matched cohort.

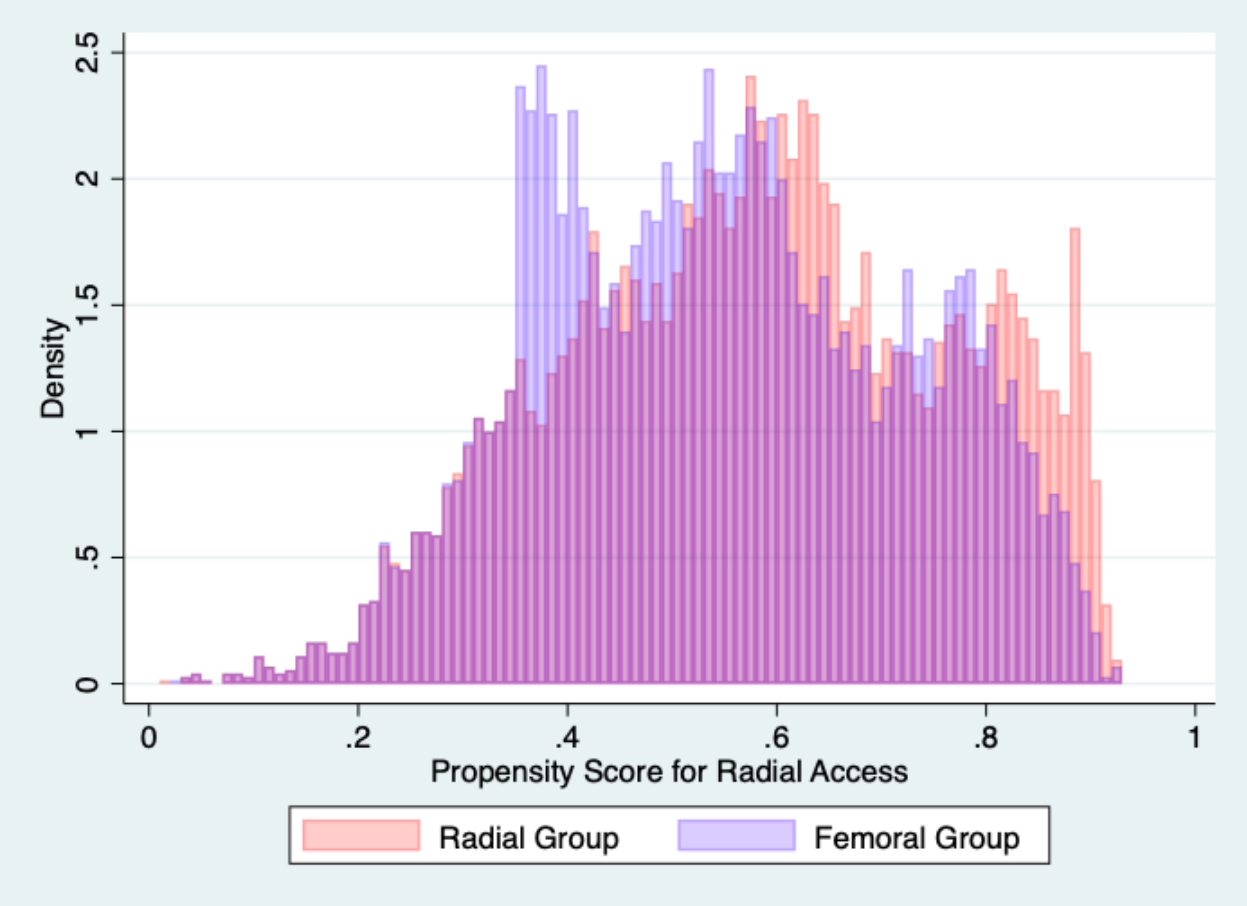

Table S1. Baseline characteristics of all patients before propensity score matching.

Characteristic	All Patients	Radial Group	Femoral Group
	N = 24463	N = 11020	N = 13430
Female - no. (%)	5652 (23.1%)	2817 (25.6%)	2826 (21.0%)
Age - mean (SD)	64.748922 (11.494138)	65.4 (11.8)	64.2 (11.2)
Chinese - no. (%)	22997 (94.0%)	10299 (93.5%)	12685 (94.5%)
Tobaco use - no. (%)	10555 (46.1%)	4523 (44.7%)	6031 (47.1%)
Diabetes mellitus - no. (%)	8540 (34.9%)	4119 (37.4%)	4418 (32.9%)
Hypertension - no. (%)	15642 (63.9%)	7289 (66.1%)	8351 (62.2%)
Dyslipidemia - no. (%)	15451 (63.2%)	6908 (62.7%)	8539 (63.6%)
Cerebrovascular disease - no. (%)	2360 (9.6%)	1286 (11.7%)	1073 (8.0%)
Chronic obstructive pulmonary disease - no. (%)	582 (2.4%)	279 (2.5%)	303 (2.3%)
Peripheral vascular disease - no. (%)	348 (1.4%)	217 (2.0%)	131 (1.0%)
History of malignancy - no. (%)	1281 (5.2%)	622 (5.6%)	659 (4.9%)
Cirrhosis - no. (%)	62 (0.3%)	29 (0.3%)	33 (0.2%)
Estimated GFR - ml/min/1.73m2, mean (SD)	80.699677 (27.543228)	77.2 (30.7)	83.6 (24.3)
Estimated GFR < 50ml/min/1.73m2 - no. (%)	2778 (11.4%)	1770 (16.1%)	1008 (7.5%)
White blood cell count - 10^9/L, mean (SD)	8.2533959 (3.0845965)	8.3 (3.3)	8.2 (2.9)
Anemia - no. (%)	7679 (31.4%)	4003 (36.3%)	3674 (27.4%)
Atrial fibrillation or flutter - no. (%)	1305 (5.3%)	659 (6.0%)	644 (4.8%)
On anti-coagulant before PCI - no. (%)	627 (2.6%)	302 (2.7%)	323 (2.4%)
Previous myocardial infarction - no. (%)	3048 (12.5%)	1474 (13.4%)	1574 (11.7%)
Previous coronary artery bypass surgery - no. (%)	422 (1.7%)	370 (3.4%)	52 (0.4%)
Previous heart failure - no. (%)	1916 (7.8%)	1037 (9.4%)	878 (6.5%)
NYHA class III-IV in last 2 weeks before PCI - no. (%)	987 (4.0%)	567 (5.1%)	420 (3.1%)
Cardiogenic shock - no. (%)	581 (2.4%)	416 (3.8%)	165 (1.2%)
Ventricular tachycardia in <48 hours before PCI - no. (%)	672 (2.7%)	427 (3.9%)	245 (1.8%)
PCI urgency - no. (%)			
Elective	14267 (58.3%)	6184 (56.1%)	8071 (60.1%)
Urgent	6739 (27.6%)	2882 (26.2%)	3856 (28.7%)
Emergent	3453 (14.1%)	1951 (17.7%)	1502 (11.2%)
Indication for PCI - no. (%)			
Stable angina	4646 (19.0%)	2014 (18.3%)	2626 (19.6%)
Unstable angina	5089 (20.8%)	2244 (20.4%)	2841 (21.2%)
Non-ST elevation myocardial infarction	11271 (46.1%)	4868 (44.2%)	6400 (47.7%)

ST elevation myocardial infarction	3450 (14.1%)	1890 (17.2%)	1560 (11.6%)
Number of major epicardial artery involved - no. (%)			
One vessel disease	11022 (45.2%)	4680 (42.7%)	6330 (47.1%)
Two vessel disease	8164 (33.5%)	3711 (33.9%)	4452 (33.2%)
Three vessel disease	5211 (21.4%)	2567 (23.4%)	2644 (19.7%)
Proportion of radial access use by institution - no. (%)			
1st quantile (lowest radial use)	9780 (40.0%)	6055 (54.9%)	3725 (27.7%)
2nd quantile	6917 (28.3%)	2637 (23.9%)	4279 (31.9%)
3rd quantile	3245 (13.3%)	1095 (9.9%)	2140 (15.9%)
4th quantile (highest radial use)	4521 (18.5%)	1233 (11.2%)	3286 (24.5%)
Year of PCI - no. (%)			
2010-2013	10138 (41.4%)	5704 (51.8%)	4432 (33.0%)
2014-2017	14325 (58.6%)	5316 (48.2%)	8998 (67.0%)

SD, standard deviation; GFR, glomerular filtration rate; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

Table S2. Procedural characteristics and medications on hospital discharge of patients before propensity score matching.

Characteristic	All Patients	Radial Group	Femoral Group
	N = 24463	N = 11020	N = 13430
Intravascular imaging - no. (%)	11972 (48.9%)	4431 (40.2%)	7539 (56.1%)
Intravascular ultrasonography - no. (%)	8618 (35.2%)	3294 (29.9%)	5323 (39.6%)
Optic coherence tomography - no. (%)	3502 (14.3%)	1169 (10.6%)	2331 (17.4%)
Angiographic success - no. (%)	23830 (97.5%)	10635 (96.7%)	13183 (98.2%)
Drop in hemoglobin >2g/dL - no. (%)	4294 (17.6%)	1850 (16.8%)	2438 (18.2%)
Anemia after PCI - no. (%)	9967 (44.8%)	5257 (50.6%)	4706 (39.7%)
Aspirin on discharge - no. (%)	23765 (97.1%)	10696 (97.1%)	13059 (97.2%)
P2Y12 inhibitor on discharge - no. (%)	24079 (98.4%)	10816 (98.1%)	13253 (98.7%)
Potent P2Y12 inhibitor on discharge - no. (%)	3798 (15.5%)	1364 (12.4%)	2433 (18.1%)
Proton pump inhibitor on discharge - no. (%)	14779 (60.4%)	6262 (56.8%)	8508 (63.4%)
P2Y12 inhibitor duration - median (IQR) in days	366 (362, 408)	365 (244, 415)	366 (364, 404)
Statin on discharge - no. (%)	23275 (95.1%)	10380 (94.2%)	12887 (96.0%)
ACE inhibitor or ARB on discharge - no. (%)	16735 (68.4%)	7773 (70.5%)	8959 (66.7%)
Beta-blocker on discharge - no. (%)	17902 (73.2%)	8358 (75.8%)	9541 (71.0%)
Anti-coagulatant on discharge - no. (%)	906 (3.7%)	436 (4.0%)	468 (3.5%)

PCI, percutaneous coronary intervention, ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker.