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Access-Site Crossover in Patients With Acute Coronary Syndrome Undergoing Invasive Management

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ABSTRACT

OBJECTIVES The aim of this study was to assess the impact of access-site crossover in patients with acute coronary syndrome undergoing invasive management via radial or femoral access.

BACKGROUND There are limited data on the clinical implications of access-site crossover.

METHODS In the MATRIX (Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox)-Access trial, 8,404 patients with acute coronary syndrome were randomized to radial or femoral access. Patients undergoing access-site crossover or successful access site were investigated. Thirty-day coprimary outcomes were a composite of death, myocardial infarction, or stroke (major adverse cardiovascular events [MACE]) and a composite of MACE or Bleeding Academic Research Consortium type 3 or 5 bleeding (net adverse clinical events [NACE]).

RESULTS Access-site crossover occurred in 183 of 4,197 patients (4.4%) in the radial group (mainly to femoral access) and 108 of 4,207 patients (2.6%) in the femoral group (mainly to radial access). In multivariate analysis, the risk for coprimary outcomes was not significantly higher with radial crossover compared with successful radial (MACE: adjusted rate ratio [adjRR]: 1.25; 95% confidence interval [CI]: 0.81 to 1.93; p = 0.32; NACE: adjRR: 1.40; 95% CI: 0.94 to 2.06; p = 0.094) or successful femoral access (MACE: adjRR: 1.17; 95% CI: 0.76 to 1.81; p = 0.47; NACE: adjRR: 1.26; 95% CI: 0.86 to 1.86; p = 0.24). Access site-related Bleeding Academic Research Consortium type 3 or 5 bleeding was higher with radial crossover than successful radial access. Femoral crossover remained associated with higher risks for MACE (adjRR: 1.84; 95% CI: 1.18 to 2.87; p = 0.007) and NACE (adjRR: 1.69; 95% CI: 1.09 to 2.62; p = 0.019) compared with successful femoral access. Results remained consistent after excluding patients with randomized access not attempted.

CONCLUSIONS Crossover from radial to femoral access abolishes the bleeding benefit offered by the radial over femoral artery but does not appear to increase the risk for MACE or NACE compared with successful radial or femoral access. (Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox [MATRIX]; NCT01433627) (J Am Coll Cardiol Intv 2021;14:361-73) © 2021 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

adjRR = adjusted rate ratio

BARC = Bleeding Academic Research Consortium

CI = confidence interval

MACE = major adverse cardiovascular event(s)

NACE = net adverse clinical event(s)

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

The radial artery is currently recommended by European and American professional societies as the default vascular access site for the invasive management of patients with acute coronary syndrome (ACS) (1,2). In randomized clinical trials and observational registries, radial access has been shown to reduce the risk for major bleeding, vascular complications, and all-cause mortality (3–6) and to improve quality of life and reduce health care costs (7) compared with femoral access. As a result, the adoption of radial access has steadily increased over time (8,9). However, in up to 10% of patients, technical difficulties related to radial intervention can preclude the use or cause the failure of radial access, requiring crossover to femoral access (3–6,10–14).

It remains unclear if access-site crossover from radial to femoral access negatively affects outcomes compared with primary successful femoral access, especially in the setting of ST-segment elevation myocardial infarction (STEMI), in which the bailout switch to a second vascular access site has been associated with delayed interventions (10,15). Similarly, no study has so far investigated the prognostic implications of crossover from femoral to radial access in invasively managed patients with ACS, which still occurs in up to 4% of cases (3–6).

We sought therefore to assess the incidence, characteristics, and prognostic implications of access-site crossover in patients with ACS undergoing invasive management by randomly allocated radial or femoral access from the MATRIX (Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox)-Access trial.

SEE PAGE 374

METHODS

STUDY DESIGN AND PARTICIPANTS. This was a prespecified subanalysis of MATRIX-Access, a randomized, multicenter, superiority trial comparing radial versus femoral access in patients with ACS, with or without ST-segment elevation, undergoing invasive management (NCT01433627). The rationale, design, and main results of the MATRIX program have been previously reported (4,5,16). In brief, patients were randomized (1:1) to radial or femoral access for diagnostic angiography and percutaneous coronary intervention (PCI) if indicated. Patients were eligible if they presented with ACS with or without ST-segment elevation, if they were about to receive invasive management, and if the interventional cardiologist was willing to proceed with either radial or femoral access with expertise for both, including at least 75 coronary interventions performed and at least 50% of interventions in patients with ACS via the radial artery during the previous year (4,16). Access-site management during and after the procedure was left to the discretion of the treating physician (16,17). The use of anticoagulant agents outside the MATRIX protocol was not allowed. Bivalirudin was administered according to the approved product labeling. Unfractionated heparin was dosed at 70 to 100 U/kg in patients not receiving glycoprotein IIb/IIIa inhibitors and 50 to 70 U/kg in patients receiving glycoprotein IIb/IIIa inhibitors. The use of all other medications was allowed per guidelines. The study protocol of the MATRIX trial was approved by institutional ethics committees of participating institutions and was conducted according to the Declaration of Helsinki and Good Clinical Practice.

ACCESS-SITE CROSSOVER DEFINITION. All participants in the MATRIX-Access trial were considered eligible for the present analysis. On the basis of the arterial access site used to perform coronary catheterization in the index procedure, patients were categorized into 4 groups: 1) radial crossover, if the operator failed to start or complete the procedure via the randomly assigned radial access and required crossover to femoral or brachial access; 2) femoral crossover, if the operator failed to start or complete the procedure via the randomly assigned femoral access and required crossover to radial or brachial access; and 3) successful radial or 4) successful femoral access, if the operator successfully performed the procedure via the randomly assigned access. Patients undergoing crossover from the radial to the ulnar artery, from the radial to the contralateral radial artery, or from the femoral to the contralateral femoral

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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TABLE 1 Baseline Characteristics of Radial and Femoral Groups

	Radial Crossover (n = 183)	Successful Radial (n = 4,014)	Femoral Crossover (n = 108)	Successful Femoral (n = 4,099)	p Value*	p Value†	p Value‡
Baseline characteristics							
Age, yrs	69.8 ± 11.3§	65.4 ± 11.8	65.5 ± 12.8	65.9 ± 11.8	<0.001	<0.001	0.68
≥75 yrs	69 (37.7)	1,004 (25.0)	30 (27.8)	1,079 (26.3)	<0.001	<0.001	0.73
Male	123 (67.2)	3,003 (74.8)	77 (71.3)	2,969 (72.4)	0.021	0.12	0.79
Body mass index, kg/m^2	27.0 ± 4.1§	27.1 ± 4.2	28.2 ± 5.7	27.0 ± 4.1	0.87	0.97	0.003
Diabetes mellitus	53 (29.0)	906 (22.6)	37 (34.3)	907 (22.1)	0.044	0.030	0.002
Insulin dependent	12 (6.6)§	197 (4.9)	15 (13.9)	242 (5.9)	0.31	0.71	<0.001
Current smoking	41 (22.4)	1,418 (35.3)	32 (29.6)	1,396 (34.1)	<0.001	0.001	0.33
Hypercholesterolemia	83 (45.4)	1,716 (42.8)	51 (47.2)	1,841 (44.9)	0.48	0.90	0.63
Hypertension	127 (69.4)	2,498 (62.2)	74 (68.5)	2,612 (63.7)	0.050	0.11	0.30
Previous myocardial infarction	39 (21.3)	546 (13.6)	22 (20.4)	596 (14.5)	0.003	0.011	0.091
Previous PCI	34 (18.6)	576 (14.3)	23 (21.3)	562 (13.7)	0.11	0.062	0.024
Previous CABG	11 (6.0)	100 (2.5)	4 (3.7)	142 (3.5)	0.003	0.069	0.89
Previous TIA or stroke	15 (8.2)	180 (4.5)	6 (5.6)	224 (5.5)	0.019	0.11	0.96
Peripheral vascular disease	17 (9.3)§	324 (8.1)	22 (20.4)	350 (8.5)	0.55	0.72	<0.001
Renal failure	8 (4.4)	38 (0.9)	3 (2.8)	56 (1.4)	<0.001	0.001	0.21
Dialysis	2 (1.1)	2 (0.1)	0 (0.0)	4 (0.1)	0.010	0.024	>0.99
Clinical presentation							
STEMI	101 (55.2)§	1,900 (47.3)	41 (38.0)	1,968 (48.0)	0.037	0.057	0.039
NSTE-ACS	82 (44.8)§	2,114 (52.7)	67 (62.0)	2,131 (52.0)			
NSTE-ACS, troponin positive	73 (39.9)§	1,881 (46.9)	64 (59.3)	1,868 (45.6)	0.064	0.13	0.004
Heart rate, beats/min	75.7 ± 15.9	76.3 ± 16.6	79.1 ± 18.7	75.9 ± 16.8	0.59	0.84	0.050
Systolic arterial pressure, mm Hg	135.4 ± 27.3	138.6 ± 25.4	139.0 ± 30.4	138.8 ± 25.5	0.095	0.078	0.94
Left ventricular ejection fraction, %	48.9 ± 11.0	51.4 ± 9.5	51.2 ± 9.8	50.8 ± 9.8	0.001	0.012	0.74
eGFR, ml/min/1.73 m^2	76.0 ± 27.4§	84.5 ± 25.3	84.7 ± 32.9	83.3 ± 25.3	<0.001	<0.001	0.57
eGFR <60 ml/min/1.73 m^2	49 (27.2)	651 (16.3)	24 (22.4)	691 (17.0)	<0.001	<0.001	0.13
Cardiac arrest at presentation	5 (2.7)	80 (2.0)	2 (2.0)	81 (2.0)	0.53	0.44	0.89
Killip class							
I	151 (82.5)	3,645 (90.8)	92 (85.2)	3,708 (90.5)			
II	20 (10.9)	248 (6.2)	11 (10.2)	290 (7.1)	<0.001	<0.001	0.27
III	2 (1.1)	86 (2.1)	4 (3.7)	75 (1.8)			
IV	10 (5.5)	35 (0.9)	1 (0.9)	26 (0.6)			
Medications before catheterization							
Lytic therapy	5 (2.7)	89 (2.2)	0 (0.0)	104 (2.5)	0.64	0.86	0.093
Aspirin	171 (93.4)	3,785 (94.3)	106 (98.1)	3,848 (93.9)	0.62	0.81	0.065
Clopidogrel	94 (51.4)	1,921 (47.9)	58 (53.7)	1,939 (47.3)	0.35	0.28	0.18
Prasugrel	18 (9.8)	467 (11.6)	10 (9.3)	458 (11.2)	0.45	0.57	0.53
Ticagrelor	42 (23.0)	936 (23.3)	19 (17.6)	1,010 (24.6)	0.90	0.60	0.092
Enoxaparin	22 (12.0)§	665 (16.6)	26 (24.1)	716 (17.5)	0.10	0.056	0.075
Fondaparinux	15 (8.2)§	413 (10.3)	17 (15.7)	451 (11.0)	0.36	0.23	0.12
ACE inhibitors	54 (29.5)	1,199 (29.9)	37 (34.3)	1,264 (30.8)	0.91	0.70	0.44
Angiotensin II receptor blocker	19 (10.4)	431 (10.7)	16 (14.8)	446 (10.9)	0.87	0.83	0.19
Statin	75 (41.0)	1,737 (43.3)	49 (45.4)	1,814 (44.3)	0.54	0.38	0.81
Beta-blocker	72 (39.3)	1,622 (40.4)	45 (41.7)	1,730 (42.2)	0.77	0.44	0.91
Warfarin	3 (1.6)	69 (1.7)	3 (2.8)	61 (1.5)	0.93	0.86	0.27
Proton pump inhibitor	92 (50.3)	2,066 (51.5)	59 (54.6)	2,133 (52.0)	0.75	0.64	0.59
Unfractionated heparin	54 (29.5)	1,185 (29.5)	22 (20.4)	1,215 (29.6)	0.99	0.96	0.036
Bivalirudin	0 (0)	4 (0.1)	0 (0.0)	2 (0.1)	>0.99	>0.99	>0.99
Glycoprotein IIb/IIIa inhibitor	0 (0)	8 (0.2)	0 (0.0)	6 (0.1)	>0.99	>0.99	>0.99

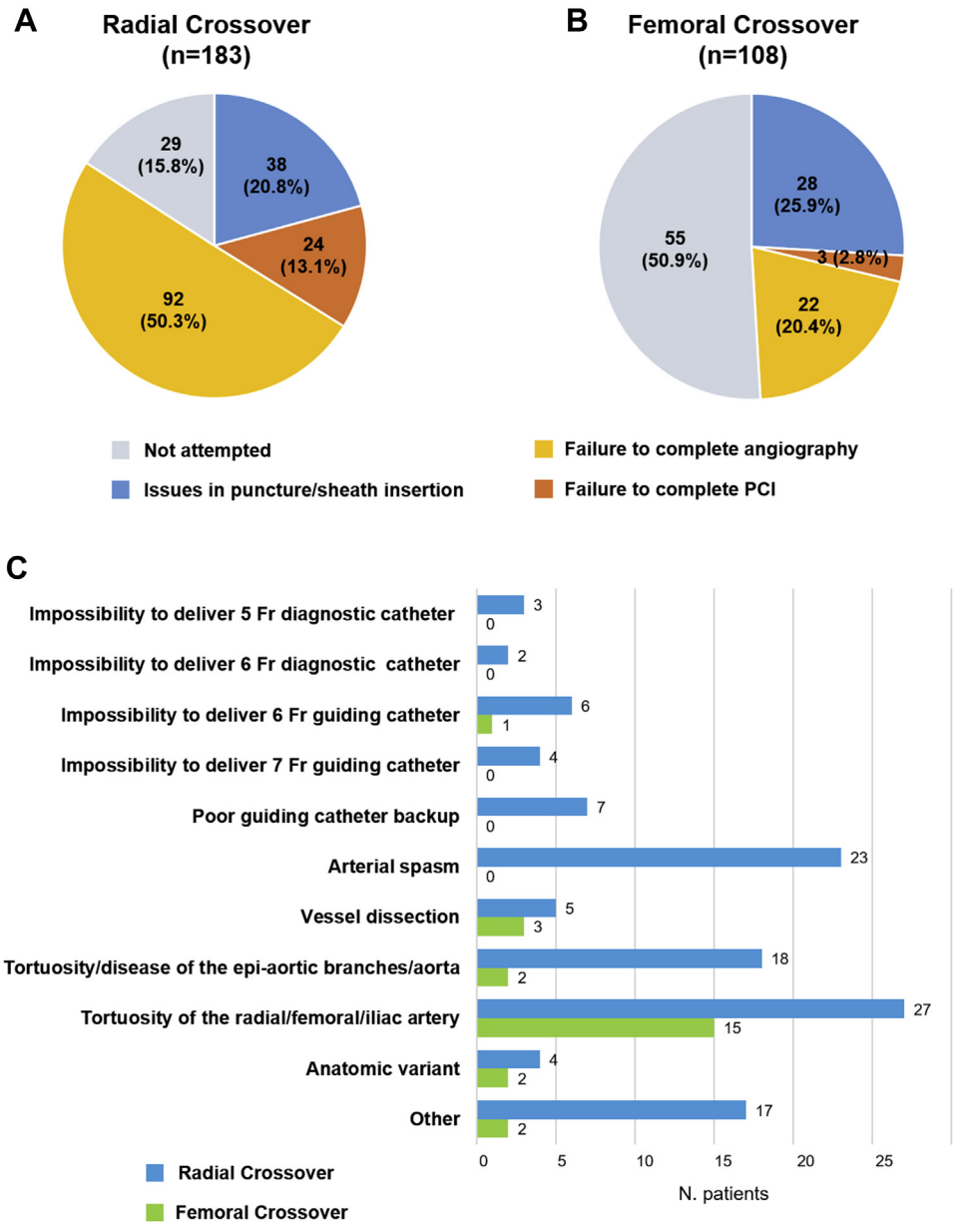
Values are mean ± SD or n (%). The p values were generated using the chi-square or Fisher exact test for categorical variables and Student's *t*-test or the Wilcoxon test for continuous variables. *For radial crossover versus successful radial access. †For radial crossover versus successful femoral access. ‡For femoral crossover versus successful femoral access. §p < 0.05, radial crossover group versus femoral crossover group.

ACE = angiotensin-converting enzyme; CABG = coronary artery bypass grafting; eGFR = estimated glomerular filtration rate; NSTE-ACS = non–ST-segment elevation acute coronary syndrome; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; TIA = transient ischemic attack.

artery (internal crossover) were not considered crossover patients. Clinical and/or procedural reasons determining radial or femoral crossover were collected and categorized as follows: 1) access site not attempted, if the randomly allocated access was not chosen by the operator as initial access for any clinical reason; 2) issues in arterial puncture or sheath insertion; 3) failure to complete coronary angiography; and 4) failure to complete PCI.

FOLLOW-UP AND STUDY OUTCOMES. In the MATRIX program, the 2 coprimary outcomes at 30 days were major adverse cardiovascular events

FIGURE 1 Crossover Data for Radial and Femoral Groups



(A) Reasons for radial access crossover. **(B)** Reasons for femoral access crossover. **(C)** Access-site issues causing crossover after successful sheath insertion in patients undergoing radial or femoral crossover. PCI = percutaneous coronary intervention.

(MACE), defined as the composite of all-cause death, myocardial infarction, or stroke, and net adverse clinical events (NACE), defined as the composite of MACE or major bleeding not related to coronary artery bypass grafting (Bleeding Academic Research Consortium [BARC] type 3 or 5) (16). Secondary outcomes included each component of the coprimary outcomes, cardiovascular death, access site-related and non-access site-related bleeding events, and definite or probable stent thrombosis. Bleeding was defined according to the BARC, TIMI (Thrombolysis In Myocardial Infarction), and GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator) scales. An independent clinical events committee, blinded to treatment allocation, adjudicated all adverse events.

STATISTICAL ANALYSIS. The MATRIX-Access trial was powered for superiority on the 2 coprimary outcomes at 30 days, expecting a rate reduction of 30% that corresponded to a rate ratio of 0.70. All analyses were performed following intention-to-treat principles, and clinical events at 30 days after randomization were considered. Primary and secondary outcomes were analyzed as time to first event using the Mantel-Cox method, accompanied by log-rank tests to calculate corresponding 2-sided p values. For the present analysis, to take into account differences in baseline characteristics among study groups, dedicated multivariate models were implemented to obtain adjusted outcomes, including as variables: 1) age, sex, diabetes, smoking, previous myocardial infarction, previous coronary artery bypass grafting, previous transient ischemic attack or stroke, type of ACS, ejection fraction, estimated glomerular filtration rate, Killip class, glycoprotein IIb/IIIa inhibitor use, intra-aortic balloon pump use, staged procedure, left main PCI, sheath size, post-procedural TIMI flow grade 3, and total contrast volume for the comparison between radial crossover and successful radial access; 2) age, diabetes, smoking, previous myocardial infarction, previous coronary artery bypass grafting, type of ACS, ejection fraction, estimated glomerular filtration rate, Killip class, glycoprotein IIb/IIIa inhibitor use, intra-aortic balloon pump use, staged procedure, left main PCI, sheath size, post-procedural TIMI flow grade 3, and total contrast volume for the comparison between radial crossover and successful femoral access; and 3) body mass index, diabetes, previous PCI, peripheral vascular disease, type of ACS, lytic therapy use, ticagrelor use before catheterization laboratory, unfractionated heparin use before catheterization laboratory, post-PCI bivalirudin regimen, sheath size, and total contrast volume for the comparison between femoral crossover and successful femoral access. Sensitivity analyses were conducted in patients undergoing access-site crossover after unsuccessful attempts via the randomly allocated access (i.e., excluding patients without initial attempts from the assigned access). Subgroups analysis according to the clinical presentation was performed to estimate possible interaction terms across comparisons. All analyses were performed using Stata version 15.1 (StataCorp, College Station, Texas).

RESULTS

STUDY POPULATION. The MATRIX-Access trial enrolled 8,404 patients, of whom 4,197 were randomized to radial access and 4,207 to femoral access. In the radial group, 4.4% of patients (n = 183) underwent crossover to femoral (n = 178) or brachial (n = 5) access, while in the femoral group, 2.6% (n = 108) of patients had crossover to radial (n = 107) or brachial (n = 1) access.

CLINICAL AND PROCEDURAL CHARACTERISTICS. Baseline and procedural characteristics of the study population are detailed in **Table 1** and Supplemental Table 1. Compared with patients undergoing successful radial access, patients with radial crossover were approximately 5 years older and more frequently women; more often had histories of myocardial infarction, coronary artery bypass grafting, and renal failure; presented more often with STEMI or advanced Killip class; and more frequently underwent left main coronary intervention, hemodynamic support, and unsuccessful PCI. Compared with patients undergoing successful femoral access, those with femoral crossover had higher body mass index, more often had histories of diabetes and peripheral vascular disease, and less frequently had diagnoses of STEMI on admission. Both crossover groups had a higher prevalence of diabetes and were exposed to higher contrast volumes and longer fluoroscopy and procedural times than patients undergoing successful access site. Compared with the femoral crossover group, patients with radial crossover were older, had lower body mass index and estimated glomerular filtration rates, presented more frequently with STEMI, and less often had TIMI flow grade 3 in all treated lesions after the intervention.

Access-site crossover characteristics are reported in **Figure 1**. In the radial group, difficulties in establishing radial access accounted for 20.8% of the crossover cases, whereas 50.3% of cases occurred during coronary angiography, mainly because of tortuosity or vasospasm.

CLINICAL OUTCOMES. Unadjusted outcomes at 30 days. Clinical outcomes at 30 days with respect to fatal, ischemic, and bleeding endpoints were seemingly worse in the radial and femoral crossover groups compared with patients undergoing successful radial or femoral access (**Tables 2 and 3,** Supplemental Tables 2 and 3).

Multivariate-adjusted outcomes at 30 days. ***Radial crossover versus successful radial access.*** After multivariate adjustment, the risks for MACE (adjusted rate ratio [adjRR]: 1.25; 95% confidence interval [CI]: 0.81 to 1.93; p = 0.32), NACE (adjRR: 1.40; 95% CI: 0.94 to 2.06; p = 0.090), and their individual components did not differ between patients undergoing radial crossover and those undergoing successful radial access. Yet radial crossover remained associated with a

TABLE 2 Coprimary and Main Secondary Adjusted and Unadjusted Outcomes in Patients With Radial Crossover Versus Successful Radial or Femoral Access

	Radial Crossover (n = 183)	Successful Radial (n = 4,014)	Successful Femoral (n = 4,099)	Unadjusted Rate Ratio (95% CI)*	p Value*	Adjusted Rate Ratio (95% CI)*	p Value*	Unadjusted Rate Ratio (95% CI)†	p Value†	Adjusted Rate Ratio (95% CI)†	p Value†
Death, myocardial infarction, or stroke	25 (13.7)	344 (8.6)	407 (10.0)	1.66 (1.08–2.53)	0.018	1.25 (0.81–1.93)	0.32	1.41 (0.93–2.16)	0.10	1.17 (0.76–1.81)	0.47
Death, myocardial infarction, stroke, BARC type 3 or 5 bleeding	32 (17.5)	378 (9.4)	463 (11.4)	1.98 (1.35–2.89)	<0.001	1.40 (0.94–2.06)	0.090	1.63 (1.12–2.37)	0.010	1.26 (0.86–1.86)	0.24
All-cause death	7 (3.8)	59 (1.5)	84 (2.1)	2.64 (1.20–5.79)	0.011	0.32 (0.10–1.02)	0.053	1.88 (0.87–4.08)	0.10	0.68 (0.22–2.07)	0.49
Myocardial infarction	18 (9.9)	281 (7.1)	316 (7.8)	1.45 (0.88–2.39)	0.13	1.34 (0.82–2.18)	0.23	1.31 (0.80–2.15)	0.28	1.28 (0.79–2.09)	0.31
Stroke	1 (0.6)	15 (0.4)	14 (0.3)	1.48 (0.20–11.24)	0.70	1.69 (0.15–19.17)	0.67	1.62 (0.21–12.32)	0.63	1.03 (0.11–9.61)	0.97
BARC type 3 or 5 bleeding	8 (4.4)	57 (1.5)	96 (2.4)	3.21 (1.52–6.75)	0.001	1.28 (0.47–3.49)	0.62	1.92 (0.93–3.97)	0.073	1.10 (0.46–2.63)	0.83
BARC type 3 or 5 bleeding, access site related	7 (3.9)	9 (0.2)	42 (1.1)	17.75 (6.56–47.98)	<0.001	9.65 (2.49–37.41)	0.001	3.84 (1.71–8.60)	<0.001	2.14 (0.79–5.76)	0.13
BARC type 3 or 5 bleeding, not access site related	1 (0.6)	48 (1.2)	54 (1.3)	0.46 (0.06–3.35)	0.43	0.19 (0.02–1.54)	0.11	0.42 (0.06–3.03)	0.37	0.27 (0.03–2.11)	0.21
BARC type 2, 3, or 5 bleeding	22 (12.1)	168 (4.2)	299 (7.4)	3.12 (1.98–4.93)	<0.001	1.80 (1.02–3.16)	0.041	1.75 (1.12–2.73)	0.013	1.26 (0.76–2.08)	0.37
BARC type 2, 3, or 5 bleeding, access site related	19 (10.5)	50 (1.2)	191 (4.7)	9.06 (5.26–15.62)	<0.001	6.65 (3.60–12.26)	<0.001	2.37 (1.46–3.85)	<0.001	1.87 (1.08–3.26)	0.026
BARC type 2, 3, or 5 bleeding, not access site related	3 (1.6)	119 (3.0)	113 (2.8)	0.56 (0.18–1.75)	0.30	0.28 (0.08–1.01)	0.051	0.60 (0.19–1.88)	0.37	0.41 (0.12–1.33)	0.13

Values are n (%), unless otherwise indicated. *For radial crossover versus successful radial access. †For radial crossover versus successful femoral access.
BARC = Bleeding Academic Research Consortium; CI = confidence interval.

significantly higher risk for bleeding—including access site-related BARC type 3 or 5 (adjRR: 9.65; 95% CI: 2.49 to 37.41; p = 0.001), overall BARC type 2, 3, or 5 (adjRR: 1.80; 95% CI: 1.02 to 3.16; p = 0.041), and access site-related BARC type 2, 3, or 5 events (adjRR: 6.65; 95% CI: 3.60 to 12.26; p < 0.001)—and surgical access site repair or transfusions (adjRR: 2.60; 95% CI: 1.01 to 6.67; p = 0.047) (**Central Illustration, Table 2**, and Supplemental Table 2).

Radial crossover versus successful femoral access. The adjusted risk for MACE (adjRR: 1.17; 95% CI: 0.76 to 1.81; p = 0.47), NACE (adjRR: 1.26; 95% CI: 0.86 to 1.86; p = 0.24), and their individual components did not differ between the radial crossover group and the successful femoral access group. The overall bleeding risk was also similar in the 2 groups, yet the risk for access site-related BARC type 2, 3, or 5 bleeding was higher in patients with radial crossover (adjRR: 1.87; 95% CI: 1.08 to 3.26; p = 0.026) (**Central Illustration, Table 2** and Supplemental Table 2).

Femoral crossover versus successful femoral access. Compared with successful femoral access, femoral crossover remained associated with a significantly increased risk for MACE (adjRR: 1.84; 95% CI: 1.18 to 2.87; p = 0.007) and NACE (adjRR: 1.69; 95% CI: 1.09 to 2.62; p = 0.019), as well as death, stroke, urgent target vessel revascularization, and definite or probable stent thrombosis after multivariate adjustment. Bleeding events did not differ between the 2 groups (**Central Illustration, Table 3** and Supplemental Table 3).

SENSITIVITY ANALYSIS. Sensitivity analyses showed consistent results in patients undergoing radial (n = 154) or femoral (n = 53) crossover after unsuccessful attempts. After excluding patients with assigned access sites not attempted, both crossover groups confirmed higher crude event rates than the successful access groups (**Table 4** and Supplemental Table 4). Compared with those undergoing successful radial access, patients with radial crossover showed a higher adjusted risk for NACE and bleeding events, related mainly to access site. The radial crossover group also showed an increased risk for access site-related BARC type 2, 3, or 5 bleeding compared with the successful femoral access group but no difference in terms of ischemic or fatal endpoints. Patients with femoral crossover had a significant and borderline increase in the risk for MACE, NACE, all-cause mortality, and BARC type 2, 3, or 5 bleeding (p = 0.049, p = 0.062, p = 0.057, and

p = 0.016, respectively) compared with those undergoing successful femoral access.

SUBGROUP ANALYSES. Subgroup analyses suggested that the type of presenting syndrome—with or without ST-segment elevation—affected the prognostic impact of access-site crossover so that the bleeding risk associated with radial crossover and the ischemic hazard associated with femoral crossover were both apparently magnified among patients with STEMI compared with patients in whom the allocated access site was successful, with positive interaction testing (Supplemental Figures 1 to 3).

DISCUSSION

To the best of our knowledge, this is the largest study investigating the incidence, characteristics, and prognostic implications of access-site crossover in patients with ACS undergoing invasive management via radial or femoral access. The key findings are the following.

First, crossover from radial to mainly femoral access occurred more frequently in patients presenting with advanced age, histories of coronary artery bypass grafting, STEMI, and more advanced Killip class. Compared with successful radial access, radial crossover was associated with a higher risk for access site–related major bleeding, which was particularly evident among patients with STEMI, to the extent that they did not differ compared with patients undergoing successful femoral access. Importantly, there was no signal of increased ischemic risk with radial crossover compared with successful radial or femoral access.

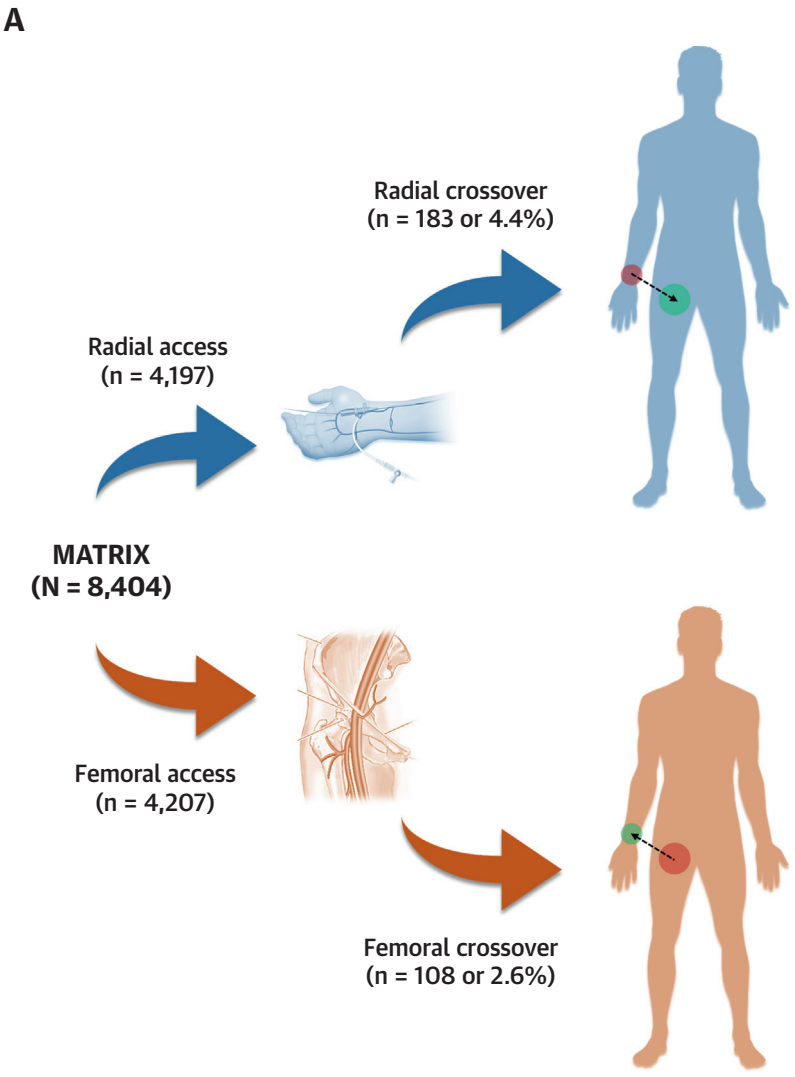
Second, crossover from femoral to mainly radial access occurred more frequently in patients with higher body mass index, established diabetes and/or peripheral artery disease, and non–ST-segment elevation ACS on admission. Femoral crossover was not associated with a higher risk for major bleeding. However, despite extensive multivariate adjustment, the risk for both coprimary endpoints, death, stroke, and stent thrombosis was higher with femoral crossover compared with successful femoral access. Subgroup analyses suggested that this risk was particularly pronounced among patients with STEMI.

European guidelines recommend the radial artery as the preferred vascular access site in patients with ACS undergoing invasive management (1). However, crossover from radial to femoral access remains a not uncommon occurrence even at highly experienced centers, and patients in whom crossover is undertaken incur a higher risk for ischemic and bleeding events (10,11,15). In this context, selecting up front the optimal access site remains essential to improving patients' management in the setting of ACS. Whether crossover is simply a marker of patient risk profile or whether it is causally related to impaired outcomes remains unclear. As a consequence, the threshold to cross over from radial to femoral access in more complex cases varies in clinical practice.

INCIDENCE AND CHARACTERISTICS OF ACCESS-SITE CROSSOVER. In contemporary PCI cohorts, radial crossover has been reported in up to 10% of cases, though this rate varies widely according patient characteristics, procedural aspects, and operator expertise (10–15,18,19). In the RIVAL (A Trial of Trans-Radial Versus Trans-Femoral Percutaneous Coronary Intervention [PCI] Access Site Approach in Patients With Unstable Angina or Myocardial Infarction Managed With an Invasive Strategy) trial (3), enrolling 7,021 patients with ACS with and without ST-segment elevation, the incidence of crossover was 7.6% in patients randomized to radial access and 2.0% in those randomized to femoral access, while in the RIFLE-STEACS (Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome) trial (6), including 1,001 patients with STEMI, the corresponding figures were 9.4% and 2.8%. In large observational studies, including patients undergoing elective or urgent coronary catheterization, access-site crossover has been reported in 4% to 8% of cases for radial access and in about 2% of cases for femoral access (10–15). In the MATRIX trial, access-site crossover occurred in 4.4% of patients randomized to radial access and 2.6% of those randomized to femoral access, and this rate did further decrease to 3.7% and 1.3%, respectively, after excluding patients in whom the randomly allocated access was not attempted by the operator. The relatively low rate of radial crossover in the MATRIX trial should be interpreted in the context of the high radial proficiency of each participating operator. Similar to previous reports, the principal reasons for crossover in our cohort were issues related to the arterial puncture or sheath insertion, vessel tortuosity, vasospasm, and the operator's decision not to attempt the randomized access (10–12).

IMPACT OF RADIAL ACCESS CROSSOVER ON PROCEDURAL AND CLINICAL OUTCOMES. A few studies have investigated procedural and clinical outcomes in patients with radial crossover compared with successful radial or femoral access (10–13,15). Among 241 patients with STEMI undergoing primary

CENTRAL ILLUSTRATION Summary of Ischemic and Bleeding Endpoints in Patients With Access-Site Crossover or Successful Access via the Radial or Femoral Artery



Gragnano, F. et al. J Am Coll Cardiol Intv. 2021;14(4):361–73.

(A) In the Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox trial, radial crossover (mainly to femoral access) and femoral crossover (mainly to radial access) occurred in 4.4% and 2.6% of cases, respectively. **(B)** Radial crossover was associated with a higher risk for Bleeding Academic Research Consortium type 3 or 5 access-site bleeding compared with successful radial access. Radial crossover abolished the bleeding benefit of radial access over femoral access but did not expose patients to higher risks for major adverse cardiovascular events (MACE) or net adverse clinical events (NACE) compared with successful femoral access. Femoral crossover was associated with a higher risk for MACE and NACE than successful femoral access. BARC = Bleeding Academic Research Consortium; MACE = major adverse cardiovascular event(s); MATRIX = Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox; NACE = net adverse clinical event(s).

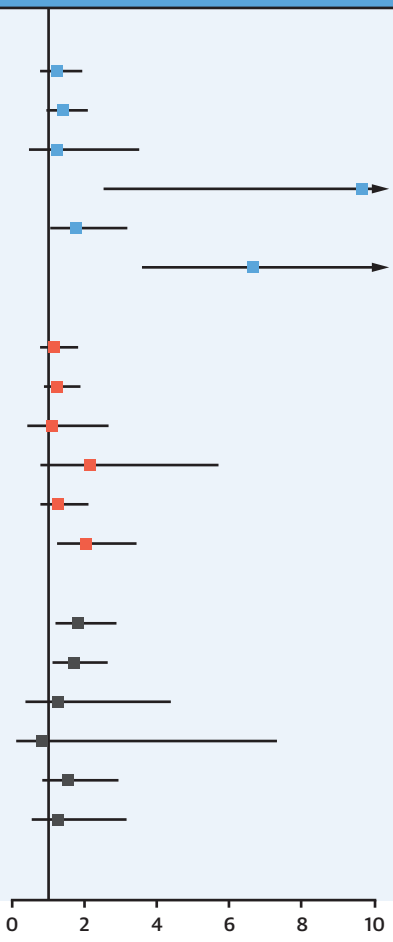
Continued on the next page

PCI (15), radial crossover was associated with a slight but significant increase in time to gain vascular access and procedure duration compared with successful radial access (of approximately 6 and 14 min, respectively) or successful femoral access (of approximately 5 and 8 min, respectively). These results are in line with our findings, as we observed a significant, although modest, increase in total procedure time, fluoroscopy time, and contrast volume (of approximately 15 min, 5 min, and 25 ml,

CENTRAL ILLUSTRATION Continued

B

Outcomes	No. of Events (%)		Multivariate Adjusted Rate Ratio (95% Confidence Interval)	p Value
Radial Crossover vs. Successful Radial Access				
MACE	25 (13.7%)	344 (8.6%)	1.25 (0.81-1.93)	0.32
NACE	32 (17.5%)	378 (9.4%)	1.40 (0.94-2.06)	0.09
BARC 3 or 5	8 (4.4%)	57 (1.5%)	1.28 (0.47-3.49)	0.62
BARC 3 or 5 access site	7 (3.9%)	9 (0.2%)	9.65 (2.49-37.41)	0.001
BARC 2, 3, or 5	22 (12.1%)	168 (4.2%)	1.80 (1.02-3.16)	0.041
BARC 2, 3, or 5 access site	19 (10.5%)	50 (1.2%)	6.65 (3.60-12.26)	< 0.001
Radial Crossover vs. Successful Femoral Access				
MACE	25 (13.7%)	407 (10.0%)	1.17 (0.76-1.81)	0.47
NACE	32 (17.5%)	463 (11.4%)	1.26 (0.86-1.86)	0.24
BARC 3 or 5	8 (4.4%)	96 (2.4%)	1.10 (0.46-2.63)	0.83
BARC 3 or 5 access site	7 (3.9%)	42 (1.1%)	2.14 (0.79-5.76)	0.13
BARC 2, 3, or 5	22 (12.1%)	299 (7.4%)	1.26 (0.76-2.08)	0.37
BARC 2, 3, or 5 access site	19 (10.5%)	191 (4.7%)	1.87 (1.08-3.26)	0.026
Femoral Crossover vs. Successful Femoral Access				
MACE	22 (20.4%)	407 (10.0%)	1.84 (1.18-2.87)	0.007
NACE	23 (21.3%)	463 (11.4%)	1.69 (1.09-2.62)	0.019
BARC 3 or 5	3 (2.9%)	96 (2.4%)	1.27 (0.37-4.35)	0.69
BARC 3 or 5 access site	1 (0.9%)	42 (1.1%)	0.83 (0.09-7.29)	0.86
BARC 2, 3, or 5	12 (11.3%)	299 (7.4%)	1.55 (0.82-2.92)	0.17
BARC 2, 3, or 5 access site	6 (5.6%)	191 (4.7%)	1.26 (0.51-3.14)	0.61



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respectively) in the 2 crossover groups compared with the successful access groups.

With respect to clinical outcomes, Abdelaal et al. (10) recently reported the prognostic impact of radial access crossover in 2,020 patients with STEMI treated with primary PCI from a single high-volume radial center. Patients requiring radial crossover (7.7% of the study population) had a higher rate of major bleeding and vascular complications, as well as 30-day mortality compared with those undergoing PCI via successful radial access. In multivariate analysis, conversion to femoral access after radial failure remained associated with a 2-fold increase in the risk for mortality (10). More data from the same center (11) as well as other institutions (15) have consistently shown that radial crossover is associated with a higher incidence of ischemic and/or bleeding events compared with successful radial access. However, these studies were potentially limited by the single-center design, the small sample size, the nonrandom allocation of access site, and the absence of adjudicated events (10,11,15). In the present analysis, including 8,404 patients with ACS from 78 centers with randomly assigned access and adjudicated endpoints, ischemic and bleeding events at 30 days were seemingly worse in both crossover groups compared with patients who underwent successful intervention via the randomly assigned access site, either the radial or femoral artery. However, the risk profile of both crossover groups was significantly worse

TABLE 3 Coprimary and Main Secondary Adjusted and Unadjusted Outcomes in Patients With Femoral Crossover Versus Successful Femoral Access

	Femoral Crossover (n = 108)	Successful Femoral (n = 4,099)	Unadjusted Rate Ratio (95% CI)	p Value	Adjusted Rate Ratio (95% CI)	p Value
Death, myocardial infarction, or stroke	22 (20.4)	407 (10.0)	2.17 (1.39–3.39)	<0.001	1.84 (1.18–2.87)	0.007
Death, myocardial infarction, stroke, BARC type 3 or 5 bleeding	23 (21.3)	463 (11.4)	1.99 (1.29–3.08)	0.001	1.69 (1.09–2.62)	0.019
All-cause death	7 (6.5)	84 (2.1)	3.24 (1.50–7.03)	0.001	3.50 (1.42–8.65)	0.006
Myocardial infarction	14 (13.3)	316 (7.8)	1.75 (1.00–3.05)	0.045	1.43 (0.83–2.44)	0.19
Stroke	2 (1.9)	14 (0.3)	5.61 (1.27–24.72)	0.010	5.31 (1.31–21.55)	0.019
BARC type 3 or 5 bleeding	3 (2.9)	96 (2.4)	1.21 (0.38–3.82)	0.74	1.27 (0.37–4.35)	0.69
BARC type 3 or 5 bleeding, access site related	1 (0.9)	42 (1.1)	0.92 (0.13–6.67)	0.93	0.83 (0.09–7.29)	0.86
BARC type 3 or 5 bleeding, not access site related	2 (1.9)	54 (1.3)	1.44 (0.35–5.89)	0.61	1.57 (0.34–7.11)	0.56
BARC type 2, 3, or 5 bleeding	12 (11.3)	299 (7.4)	1.58 (0.88–2.85)	0.12	1.55 (0.82–2.92)	0.17
BARC type 2, 3, or 5 bleeding, access site related	6 (5.6)	191 (4.7)	1.21 (0.53–2.77)	0.64	1.26 (0.51–3.14)	0.61
BARC type 2, 3, or 5 bleeding not access site related	6 (5.7)	113 (2.8)	2.08 (0.91–4.76)	0.074	1.85 (0.74–4.61)	0.18

Values are n (%), unless otherwise indicated. Rate ratios and p values are for femoral crossover versus successful femoral access.
Abbreviations as in Table 2.

compared with the successful access site groups. After extensive adjustment for all measured confounders, radial crossover was no longer associated with higher ischemic risk compared with successful radial or femoral access. Yet radial crossover remained associated with a higher risk for access site-related major and minor bleeding compared with successful radial access to the extent that this subset of patients incurred at least the same risk for access site-related major bleeding compared with patients successfully treated via femoral access. These results remained consistent after excluding patients in whom the operator elected not to attempt the randomized access for clinical reasons. Our findings can be easily explained by the need to puncture a second femoral or brachial access site, and both alternatives

TABLE 4 Coprimary and Main Secondary Adjusted Outcomes in Patients With Access-Site Crossover After Initial Attempts Versus Successful Access

	Radial Crossover (n = 154)	Successful Radial (n = 4,014)	Femoral Crossover (n = 53)	Successful Femoral (n = 4,099)	Adjusted Rate Ratio (95% CI)*	p Value*	Adjusted Rate Ratio (95% CI)†	p Value†	Adjusted Rate Ratio (95% CI)‡	p Value‡
Death, myocardial infarction, or stroke	22 (14.3)	344 (8.6)	12 (22.6)	407 (10.0)	1.32 (0.83–2.08)	0.23	1.25 (0.79–1.98)	0.34	1.78 (1.01–3.16)	0.049
Death, myocardial infarction, stroke, BARC type 3 or 5 bleeding	29 (18.8)	378 (9.4)	13 (24.5)	463 (11.4)	1.53 (1.02–2.30)	0.037	1.38 (0.92–2.07)	0.11	1.71 (0.97–3.01)	0.062
All-cause death	6 (3.9)	59 (1.5)	3 (5.7)	84 (2.1)	0.42 (0.12–1.47)	0.17	1.08 (0.36–3.28)	0.88	3.22 (0.96–10.73)	0.057
Myocardial infarction	16 (10.5)	281 (7.1)	9 (17.3)	316 (7.8)	1.37 (0.81–2.31)	0.23	1.30 (0.76–2.20)	0.33	1.55 (0.80–2.99)	0.19
Stroke	1 (0.7)	15 (0.4)	1 (2.0)	14 (0.3)	1.83 (0.15–21.82)	0.63	1.41 (0.16–12.55)	0.75	4.24 (0.67–26.71)	0.12
BARC type 3 or 5 bleeding	8 (5.3)	57 (1.5)	2 (3.8)	96 (2.4)	1.81 (0.68–4.80)	0.23	1.34 (0.55–3.27)	0.52	1.50 (0.33–6.80)	0.60
BARC type 3 or 5 bleeding, access site related	7 (4.6)	9 (0.2)	1 (1.9)	42 (1.1)	13.16 (3.73–46.47)	0.0001	2.56 (0.92–7.12)	0.071	1.57 (0.17–14.19)	0.68
BARC type 3 or 5 bleeding, not access site related	1 (0.7)	48 (1.2)	1 (1.9)	54 (1.3)	0.25 (0.03–2.06)	0.19	0.34 (0.04–2.70)	0.30	1.37 (0.17–11.15)	0.77
BARC type 2, 3, or 5 bleeding	21 (13.8)	168 (4.2)	8 (15.3)	299 (7.4)	2.01 (1.13–3.57)	0.017	1.39 (0.82–2.35)	0.22	2.39 (1.18–4.88)	0.016
BARC type 2, 3, or 5 bleeding, access site related	19 (12.5)	50 (1.2)	5 (9.5)	191 (4.7)	7.76 (4.19–14.36)	<0.0001	2.20 (1.25–3.87)	0.0061	2.50 (0.98–6.37)	0.054
BARC type 2, 3, or 5 bleeding, not access site related	2 (1.3)	119 (3.0)	3 (5.7)	113 (2.8)	0.21 (0.05–1.01)	0.051	0.31 (0.07–1.30)	0.10	1.94 (0.62–6.07)	0.25

Values are n (%), unless otherwise indicated. *For radial crossover after initial attempts versus successful radial access. †For radial crossover after initial attempts versus successful femoral access. ‡For femoral crossover after initial attempts versus successful femoral access.
Abbreviations as in Table 2.

have been associated with a higher risk for bleeding compared with the radial artery (3–5,19). Altogether, our results are reassuring and support the concept of the radial-first strategy, considering that failure to complete the intervention via the radial artery requiring crossover to femoral access does not expose patients to heightened risks for ischemic outcomes, while understandably dissipating the bleeding benefit observed with radial access. In this context, the upfront identification of patients at high risk for radial crossover could allow operators to anticipate technical difficulties and select optimal access site in each individual patient. However, no standardized and validated tool exists to predict the risk for radial crossover and/or select specific patient cohorts that could be better treated via primary femoral access. Hence, future research addressing this issue remains desirable.

PROGNOSTIC IMPLICATIONS OF FEMORAL ACCESS CROSSOVER. No study has so far investigated the prognostic implications of femoral access crossover in invasively managed patients with ACS. Failure to accomplish a coronary procedure via the femoral access is relatively rare, and its frequency approximates 2% in large ACS cohorts (3,6,14), which is consistent with our data. In our study, patients undergoing femoral crossover were characterized by higher body mass index and more frequent histories of diabetes and peripheral artery disease compared with those with successful femoral intervention. The need for crossover from the femoral access identified a subset of patients in whom the crude incidence of composite ischemic and/or bleeding events at 30 days exceeded 20%, the highest among all study groups. After extensive adjustment, we observed an increased risk for nonfatal cardiovascular ischemic and fatal events in this group of patients compared with the successful femoral access group, which occurred mainly among patients with STEMIs. Patients with initial attempts for femoral access incurred greater ischemic risk as well as BARC type 2, 3, or 5 bleeding, attributable mainly to the originally attempted access site. Our study by design cannot prove causation, and it remains therefore unclear if and to what extent our findings reflect the presence of unmeasured confounders in this highly selected patient subset. Yet femoral crossover identified a high-risk patient population whose worse outcomes do not seem to be accounted for by baseline characteristics. Strategies to optimize femoral access management should be routinely implemented to minimize the risk for femoral access failure and subsequent complications.

STUDY LIMITATIONS. Although the present analysis is the largest evaluating patients undergoing radial or femoral access with and without crossover, MATRIX-Access was not powered to explore differences in outcomes across these subgroups. As such, the present analysis might be subject to type II error. In a non-negligible proportion of patients, especially in the femoral group, access-site crossover followed the operator's decision not to proceed via the randomly assigned access. Of note, study results remained largely consistent after excluding these cases, suggesting that our conclusions are valid and can be similarly applied to crossover patients with or without attempted access site. Access-site management was left to the discretion of the operator. Thus, all procedures related to patient preparation, puncture technique, medications (i.e., spasmolytic cocktail), and materials were used per local practice. This introduces a certain variability but reflects current practice, in which these procedures remain not standardized. Our data and conclusions apply to the context of the MATRIX trial, in which all participating centers were experienced with both radial and femoral access; therefore, similar results may not apply in centers with low radial or femoral expertise.

CONCLUSIONS

Radial access failure and subsequent crossover to femoral access abolishes the peri-procedural bleeding benefit associated with radial over femoral interventions but does not expose patients to a higher risk for MACE or NACE compared with successful radial or femoral access. In turn, femoral access failure and subsequent crossover to radial access remained associated with worse fatal and nonfatal ischemic outcomes, particularly among patients with STEMI, which could not be explained by measured patient characteristics. Although in a relevant proportion of patients undergoing femoral crossover, the randomly assigned access was not attempted by the operators, introducing potential bias, our findings remained consistent after excluding these cases in a sensitivity analysis. Our results lend further support to use of the radial artery as the default approach in patients with ACS.

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PERSPECTIVES

WHAT IS KNOWN? It remains unclear whether access-site crossover, which occurs in a sizable proportion of patients with ACS undergoing invasive management, adversely affects clinical outcomes compared with successful access.

WHAT IS NEW? Access-site crossover from radial to femoral access abolishes the bleeding benefit offered by the radial over the femoral artery but does not seem to increase the risk for MACE or NACE compared with primary successful radial or femoral access. Femoral access crossover remains associated with an increased adjusted risk for fatal events and nonfatal ischemic outcomes, particularly among patients with STEMIs.

WHAT IS NEXT? Prospective and adequately powered studies are needed to clarify the prognostic implications of access-site crossover in patients with ACS undergoing invasive management. Further research is needed to develop standardized algorithms or tools to predict the risk for access-site crossover, inform operators with respect to possible procedural difficulties, and ultimately improve access-site management and patient outcomes.

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KEY WORDS acute coronary syndrome, crossover, femoral access, percutaneous coronary intervention, radial access

APPENDIX For supplemental tables and figures, please see the online version of this paper.