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Effects of Radial Versus Femoral Artery Access in Patients With Acute Coronary Syndromes With or Without ST-Segment Elevation

Shamir R. Mehta, MD, MSc,* Sanjit S. Jolly, MD, MSc,* John Cairns, MD,† Kari Niemela, MD, PhD,‡ Sunil V. Rao, MD,§ Asim N. Cheema, MD, PhD,‖ Philippe Gabriel Steg, MD,¶ Warren J. Cantor, MD,# Vladimír Džavík, MD,** Andrzej Budaj, MD, PhD,†† Michael Rokoss, MD,* Vicent Valentin, MD,‡‡ Peggy Gao, MSc,* Salim Yusuf, MBBS, DPhil,* for the RIVAL Investigators

Hamilton, Toronto, Newmarket, Ontario, Vancouver, British Columbia, Canada; Tampere, Finland; Durham, North Carolina; Paris, France; Warsaw, Poland; and Valencia, Spain

Objectives The purpose of this study was to determine the consistency of the effects of radial artery access in patients with ST-segment elevation myocardial infarction (STEMI) and in those with non–ST-segment elevation acute coronary syndrome (NSTEACS).

Background The safety associated with radial access may translate into mortality benefit in higher-risk patients, such as those with STEMI.

Methods We compared efficacy and bleeding outcomes in patients randomized to radial versus femoral access in RIVAL (RadIal Vs femorAL access for coronary intervention trial) (N = 7,021) separately in those with STEMI (n = 1,958) and NSTEACS (n = 5,063). Interaction tests between access site and acute coronary syndrome type were performed.

Results Baseline characteristics were well matched between radial and femoral groups. There were significant interactions for the primary outcome of death/myocardial infarction/stroke/non–coronary artery bypass graft–related major bleeding (p = 0.025), the secondary outcome of death/myocardial infarction/stroke (p = 0.011) and mortality (p = 0.001). In STEMI patients, radial access reduced the primary outcome compared with femoral access (3.1% vs. 5.2%; hazard ratio [HR]: 0.60; p = 0.026). For NSTEACS, the rates were 3.8% and 3.5%, respectively (p = 0.49). In STEMI patients, death/myocardial infarction/stroke were also reduced with radial access (2.7% vs. 4.6%; HR 0.59; p = 0.031), as was all-cause mortality (1.3% vs. 3.2%; HR: 0.39; p = 0.006), with no difference in NSTEACS patients. Operator radial experience was greater in STEMI versus NSTEACS patients (400 vs. 326 cases/year, p < 0.0001). In primary PCI, mortality was reduced with radial access (1.4% vs. 3.1%; HR: 0.46; p = 0.041).

Conclusions In patients with STEMI, radial artery access reduced the primary outcome and mortality. No such benefit was observed in patients with NSTEACS. The radial approach may be preferred in STEMI patients when the operator has considerable radial experience. (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 [RIVAL]; NCT01014273) (J Am Coll Cardiol 2012;60:2490–9) © 2012 by the American College of Cardiology Foundation

From the *McMaster University and Population Health Research Institute, Hamilton Health Sciences, Hamilton, Ontario, Canada; †University of British Columbia, Vancouver, British Columbia, Canada; ‡Tampere University Hospital and Heart Centre, Tampere, Finland; §Duke Clinical Research Institute, Duke University, Durham, North Carolina; ‖St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada; ¶INSERM U-698, Recherche Clinique en Athérothrombose, Université Paris 7 and Assistance Publique–Hôpitaux de Paris, Paris, France; #Southlake Regional Health Center, Newmarket, Ontario, Canada; **University Health Network, University of Toronto, Toronto, Ontario, Canada; ††Department of Cardiology, Postgraduate Medical School, Grochowski Hospital, Warsaw, Poland; and the ‡‡Hospital Universitari Dr. Peset, Valencia, Spain. RIVAL was funded by a grant from the Canadian Network and Centre for Trials Internationally (CANNECTIN), an initiative of the Canadian Institutes of Health Research. RIVAL began as an investigator-initiated substudy of the CURRENT OASIS 7 trial, which was funded by a grant to the Population Health Research Institute (PHRI) from Sanofi and Bristol-Myers Squibb. Dr. Mehta has received an institutional research grant (to

An invasive strategy including percutaneous coronary intervention (PCI) improves clinical outcomes in patients with ST-segment elevation myocardial infarction (STEMI) and in high-risk patients with non–ST-segment elevation acute coronary syndromes (NSTEACS) (1,2). However, because these patients are also treated with multiple antithrombotic and antiplatelet therapies, they are at increased risk of bleeding complications. Bleeding has been linked with higher mortality in several large observational studies (3–5). Randomized trials have suggested that antithrombotic treatments with fewer bleeding complications may lead to improved longer-term clinical outcomes, including mortality (6–8). In observational studies of patients undergoing PCI, radial artery access reduced access site–related bleeding compared with femoral artery access (9–12), and in some studies, this benefit was strongly associated with improvements in mortality (13–16). However, these observational studies are limited by unmeasured confounding and selection bias; there have been very few randomized trials to adequately evaluate this relationship.

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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) was a multinational randomized trial involving 7,021 patients with either NSTEACS or STEMI that tested the hypothesis that a radial artery approach would reduce bleeding and major cardiovascular events compared with a femoral approach (17). There was no significant difference in the primary composite outcome of death, myocardial infarction (MI), stroke or non–coronary artery bypass graft (CABG) –related major bleeding, although there was a substantial reduction in major vascular access site complications favoring the radial approach. However, patients with STEMI differ from those with NSTEACS because they are exposed to more potent antithrombotic therapies, have higher risk-adjusted rate of bleeding complications (18), and undergo PCI with much higher frequency than patients with NSTEACS. We therefore hypothesized that there might be differences in treatment effect of radial versus femoral artery access site in patients with STEMI and NSTEACS enrolled in RIVAL.

Abbreviations and Acronyms

CABG = coronary artery bypass graft
HR = hazard ratio
MI = myocardial infarction
NSTEACS = non–ST-segment elevation acute coronary syndrome
NSTEMI = non–ST-segment elevation myocardial infarction
PCI = percutaneous coronary intervention
STEMI = ST-segment elevation myocardial infarction

Methods

Study design and patients. RIVAL was a randomized, parallel-group, multicenter trial of radial versus femoral access site intervention (17). The study protocol was previously reported (19,20). Briefly, patients were included if they had either STEMI or NSTEACS and a planned invasive approach, and the interventional cardiologist was willing to proceed with either radial or femoral access (and had expertise in both, including at least 50 radial procedures within the previous year). Patients were required to have intact dual circulation of the hand as assessed by an Allen's test. Patients were ineligible if they had cardiogenic shock, severe peripheral vascular disease precluding a femoral approach, or previous coronary bypass surgery with an internal mammary artery graft. The study was approved by all appropriate national regulatory authorities and the ethics committees of participating centers. All patients provided written informed consent to participate before enrollment.

Patients were randomly assigned to radial or femoral access by a 24-h computerized, central automated voice response system. This pre-specified analysis of the trial evaluates outcomes separately in patients with a pre-randomization diagnosis of STEMI or NSTEACS. STEMI patients were defined as those presenting with ischemic symptoms >20 min with ST-segment elevation of >2 mm in 2 contiguous pre-cordial leads or >1 mm in 2 contiguous limb leads or new left bundle branch block. Patients with NSTEACS were required to have unstable ischemic symptoms and electrocardiographic changes compatible with new ischemia or increased cardiac biomarkers. Patients 60 years of age and younger with normal cardiac biomarkers were also eligible if they had documented evidence of coronary artery disease. The primary efficacy outcome of RIVAL was the occurrence of death, myocardial infarction, stroke, or non-CABG–related major bleeding within 30 days. Key secondary outcomes were: 1) death, myocardial infarction, or stroke; and 2) non-CABG–related major bleeding at 30 days. Other secondary outcomes included components of the primary outcome and major vascular access site complications.

PHRI) from Sanofi-Aventis and Bristol-Myers Squibb; and consulting fees/honoraria (modest) from Abbott Vascular, Sanofi-Aventis, Eli Lilly, and AstraZeneca. Dr. Jolly has received an institutional research grant (to PHRI) from Sanofi-Aventis and Bristol-Myers Squibb and Medtronic; and consulting fees (modest) from Sanofi-Aventis, GlaxoSmithKline, Boehringer Ingelheim, and AstraZeneca. Dr. Cairns has recently chaired or has been a member of the Data and Safety Monitoring Boards of the following industry-sponsored trials: PALLAS (Sanofi-Aventis), ACTIVE trials (Sanofi-Aventis), AVERROES (BMS); he provides advice to Boehringer Ingelheim Canada and is a steering committee member of the TOTAL trial, which receives funding from Medtronic, Canada. Dr. Budaj has received consulting fees (modest) from Sanofi-Aventis, Eli Lilly, Novartis, AstraZeneca, and Merck; and grants from Sanofi Aventis, Boehringer Ingelheim, GlaxoSmithKline, Bristol-Myers Squibb, and AstraZeneca. Dr. Rao has received consultancy (modest) for Terumo Medical, Medicines Company, Eli Lilly, and Zoll. Dr. Steg has received institutional research grants from Servier; consulting to or honoraria (modest) from Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo-Lilly, GlaxoSmithKline, Merck, Otsuka, Roche, Sanofi-Aventis, Servier, and The Medicines Company; and has stock options in Aterovax. Dr. Džavík is a consultant to Abbott Vascular, Cordis, and Johnson & Johnson. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Detailed outcome definitions were previously reported (19,20). In brief, major bleeding was defined as bleeding that 1) was fatal; 2) resulted in transfusion of ≥2 units of blood; 3) caused substantial hypotension with the need for inotropes; 4) needed surgical intervention; 5) caused severely disabling sequelae; 6) was intracranial and symptomatic or intraocular and led to significant visual loss; or 7) led to a decrease in hemoglobin of at least 50 g/l. ACUITY (Acute Catheterization and Urgent Intervention strategy) non-CABG–related major bleeding was defined as RIVAL major bleeding, large hematomas (greater than what would be normally be expected), and pseudoaneurysms requiring intervention. Minor bleeding was defined as bleeding events that did not meet the criteria for a major bleed and required transfusion of 1 unit of blood or modification of the drug regimen (i.e., cessation of antiplatelet or antithrombotic therapy). Major vascular access site complications included a pseudoaneurysm needing closure, a large hematoma, an arteriovenous fistula, or an ischemic limb needing surgery. These complications were classified as a major bleeding event only they also met the above definition of major bleeding.

Statistical analyses. Categorical variables in each cohort and between cohorts were compared by the chi-square test and continuous variables by the Student *t* test (for normally distributed variables) or nonparametric Wilcoxon sum rank test (for non-normally distributed variables). All analyses were by intention to treat (assignment to either radial or femoral access). Outcomes of patients randomized to radial versus femoral artery access were stratified according to pre-randomization diagnosis STEMI or NSTEACS. Cumulative event rates were determined from time-to-event data and are displayed through the use of Kaplan-Meier plots. Comparisons between groups were made using of the log-rank test. Tests for interaction were performed to determine whether there was heterogeneity in treatment effect of radial versus femoral access site with pre-randomization diagnosis (STEMI vs. NSTEACS). A multivariable analysis using a Cox proportional hazards model was performed to examine whether the statistical interaction between treatment and pre-randomization diagnosis on mortality was independent of baseline variables, operator, and center volume.

Results

We enrolled a total of 7,021 patients with ACS; 1,958 with a pre-randomization diagnosis of STEMI and 5,063 patients with NSTEACS. Compared with patients with NSTEACS, patients with STEMI were younger and more

Table 1 Baseline Characteristics and Treatments in Hospital

	STEMI (n = 1,958)			NSTEACS (n = 5,063)			
	Radial (n = 955)	Femoral (n = 1,003)	p Value	Radial (n = 2,552)	Femoral (n = 2,511)	p Value	p Value STEMI vs. NSTEACS
Age, yrs	60 ± 12.0	59 ± 11.7	0.2679	63 ± 11.3	63 ± 11.7	0.9274	<0.0001
Age >75 yrs	123 (12.9)	106 (10.6)	0.1117	383 (15.0)	423 (16.8)	0.0739	<0.0001
Women	193 (20.2)	217 (21.6)	0.4383	715 (28.0)	736 (29.3)	0.3087	<0.0001
Diabetes	177 (18.5)	168 (16.7)	0.3003	604 (23.7)	554 (22.1)	0.1740	<0.0001
Previous MI	87 (9.1)	103 (10.3)	0.3864	571 (22.4)	519 (20.7)	0.1399	<0.0001
Previous PCI	57 (6.0)	66 (6.6)	0.5771	374 (14.7)	342 (13.6)	0.2906	<0.0001
Current smoker	414 (43.4)	415 (41.4)	0.3767	669 (26.2)	682 (27.2)	0.4468	<0.0001
Peripheral arterial disease	16 (1.7)	20 (2.0)	0.5999	75 (2.9)	62 (2.5)	0.3030	0.0355
Treatment in hospital							
Aspirin	953 (99.8)	998 (99.5)	0.2840	2,526 (99.0)	2,491 (99.2)	0.4045	0.0167
Clopidogrel	935 (97.9)	985 (98.2)	0.6310	2433 (95.3)	2,373 (94.5)	0.1771	<0.0001
Clopidogrel loading dose >300 mg*	448 (54.3)	427 (50.7)	0.1422	760 (51.1%)	738 (49.0)	0.2346	0.1103
UFH	674 (70.6)	657 (65.5)	0.0162	1,096 (42.9)	1,087 (43.3)	0.8055	<0.0001
LMWH	402 (42.1)	450 (44.9)	0.2163	1,404 (55.0)	1,369 (54.5)	0.7232	<0.0001
Fondaparinux	53 (5.5)	46 (4.6)	0.3307	330 (12.9)	335 (13.3)	0.6657	<0.0001
Bivalirudin	22 (2.3)	41 (4.1)	0.0253	54 (2.1)	68 (2.7)	0.1696	0.0580
GP IIb/IIIa inhibitor	329 (34.5)	312 (31.1)	0.1150	558 (21.9)	532 (21.2)	0.5571	<0.0001
Fibrinolytic therapy	121 (12.7)	112 (11.2)	0.3043	—	—	—	—
PPIs	338 (35.4)	381 (38.0)	0.2341	712 (27.9)	716 (28.5)	0.6269	<0.0001
Beta-blockers	834 (87.3)	889 (88.6)	0.3747	2,270 (88.9)	2,241 (89.2)	0.7342	0.1904
ACE inhibitors	791 (82.8)	814 (81.2)	0.3364	1,755 (68.8)	1,725 (68.7)	0.9560	<0.0001
Angiotensin receptor antagonists	57 (6.0)	67 (6.7)	0.5183	320 (12.5)	319 (12.7)	0.8598	<0.0001
Statins	910 (95.3)	969 (96.6)	0.1372	2,399 (94.0)	2,320 (92.4)	0.0227	<0.0001
Calcium-channel blockers	105 (11.0)	97 (9.7)	0.3358	550 (21.6)	526 (20.9)	0.5995	<0.0001

Values are mean ± SD or n (%). *STEMI: 825 in the radial group and 842 in the femoral group. NSTEACS: 1,486 in the radial group and 1,507 in the femoral group.

ACE = angiotensin-converting enzyme; GP = glycoprotein; LMWH = low molecular weight heparin; MI = myocardial infarction; PCI = percutaneous coronary intervention; PPIs = proton pump inhibitors; NSTEACS = non–ST-segment acute coronary syndromes; STEMI = ST-segment elevation myocardial infarction; UFH = unfractionated heparin.

likely to be male and to smoke (Table 1). They also had lower rates of previous diabetes, MI, and PCI. STEMI patients had significantly greater use of glycoprotein IIb/IIIa inhibitors, clopidogrel, and heparin, whereas fondaparinux and bivalirudin were used more commonly in patients with NSTEACS. Fibrinolytic therapy was used in 12% of patients with STEMI and in no patients with NSTEACS. Characteristics of the randomized treatment groups were well matched in each cohort with the exception of unfractionated heparin, which was used more commonly in STEMI patients allocated to radial access, and bivalirudin, which was used more commonly in STEMI patients to allocated femoral access (Table 1).

Procedures and operator experience. STEMI patients had much higher rates of PCI compared with NSTEACS patients (85% vs. 59%, $p < 0.0001$) (Table 2). In the STEMI group, operators had significantly more experience in radial artery access (median, 400 radial procedures/year) than operators in the NSTEACS group (median of 326 radial procedures/year, $p < 0.0001$). By contrast, femoral artery experience was higher among operators performing procedures in patients with NSTEACS cohort (median, 428 procedures/year) compared with operators in the STEMI patients (300 procedures/year, $p < 0.0001$). Total PCI volume was similar between STEMI and NSTEACS operators (median, 300 vs. 300 procedures/year). Drug-eluting stents were used almost twice as frequently in NSTEACS patients (44%) compared with STEMI patients (23%).

Procedural characteristics were well matched between the radial versus femoral artery randomized groups with no significant differences except for sheath sizes, which were smaller in the radial group compared with the femoral group and the use of drug-eluting stents in the NSTEACS population, which was slightly more common among patients randomized to the radial approach (Table 2). There were no significant differences in operator procedure volume between the radial and femoral groups.

Primary and secondary outcomes. For the primary outcome of death, MI, stroke or non-CABG–related major bleeding, there was a significant interaction ($p = 0.025$) between randomized treatment (radial or femoral artery access) and pre-randomization diagnosis (STEMI or NSTEACS) (Fig. 1, Table 3). We also found significant interactions for the secondary composite of death, MI, or stroke ($p = 0.011$) and for mortality alone ($p = 0.001$).

Among STEMI patients, the primary outcome occurred in 3.1% of patients randomized to radial access compared

Table 2 Procedural Characteristics and Operator Experience

Characteristic	STEMI			NSTEACS			STEMI vs. NSTEACS p Value
	Radial (n = 955)	Femoral (n = 1,003)	p Value	Radial (n = 2,552)	Femoral (n = 2,511)	p Value	
Coronary angiography	157 (16.4)	178 (17.7)	0.4427	1,135 (44.5)	1,075 (42.8)	0.2328	<0.0001
PCI	825 (86.4)	842 (83.9)	0.1293	1,486 (58.2)	1,507 (60.0)	0.1959	<0.0001
Primary PCI	702 (73.5)	749 (74.7)	0.5553	—	—	—	—
Secondary PCI	253 (26.5)	254 (25.3)	—	—	—	—	—
Stent*	778 (94.3)	807 (95.8)	0.1460	1,409 (94.8)	1,426 (94.6)	0.8132	0.5941
Bare-metal stent	608 (78.1)	642 (79.6)	0.4935	820 (58.2)	902 (63.3)	0.0058	<0.0001
>1 Drug-eluting stent	184 (23.7)	180 (22.3)	0.5243	651 (46.2)	592 (41.5)	0.0119	<0.0001
CABG	22 (2.3)	34 (3.4)	0.1495	286 (11.2)	257 (10.2)	0.2638	<0.0001
Arterial sheath size, F†							
≤5	69 (7.2)	26 (2.6)	<0.0001	436 (17.1)	211 (8.4)	<0.0001	<0.0001
6	872 (91.4)	925 (92.7)	0.2955	1,836 (72.1)	1,886 (75.2)	0.0136	<0.0001
7	13 (1.4)	45 (4.5)	<0.0001	22 (0.9)	167 (6.7)	<0.0001	0.1177
Intra-aortic balloon pump	7 (0.7)	16 (1.6)	0.0767	24 (0.9)	21 (0.8)	0.6931	0.2727
Fluoroscopy time	9.3 (6.0–15.0)	8.0 (5.0–13.0)	<.0001	9.3 (5.1–15.0)	8.0 (4.0–13.0)	<.0001	0.0130
Contrast use, ml	180 (150–220)	180 (140–220)	0.2223	190 (140–250)	190 (150–250)	0.5463	0.0005
Primary PCI time intervals	n = 643	n = 678					
Door to PCI start	85 (54–175)	85 (50–160)	0.2097				
Door to PCI end	128 (89–221)	120 (80–200)	0.0968				
Randomization to PCI start	21 (13–33)	20 (11–30)	0.0160				
Randomization to PCI end	58 (44–80)	53 (40–73)	0.0009				
Operator experience, yrs							
Radial cath or PCI	400 (225–750)	400 (210–720)	0.4152	338 (165–516)	320 (160–477)	0.4697	<.0001
Femoral cath or PCI	300 (132–523)	300 (125–523)	0.5101	420 (210–665)	436 (220–665)	0.8042	<.0001
Total PCI	300 (180–450)	300 (180–421)	0.5074	300 (190–400)	295 (190–400)	0.9303	0.2250
Proportion radial, %	50 (33–80)	47 (30–80)	0.4002	40 (20–65)	40 (20–65)	0.6355	<.0001

Values are n (%) or median (interquartile range). *As a proportion of patients undergoing PCI. †STEMI: 954 in the radial group and 998 in the femoral group. NSTEACS: 2,545 in the radial group and 2,508 in the femoral group.

CABG = coronary artery bypass graft; cath = catheterization; IQR = interquartile range; other abbreviations as in Table 1.

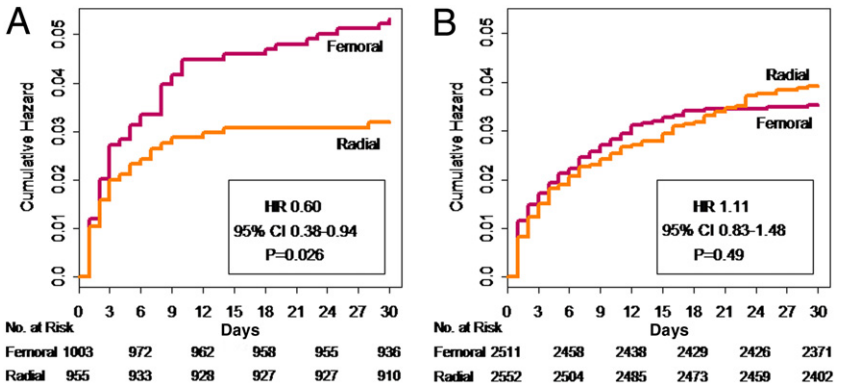

Figure 1 **Primary Outcome (Cardiovascular Death, Myocardial Infarction, Stroke, or Non-Coronary Artery Bypass Graft–Related Major Bleeding) in Patients With STEMI and NSTEACS**

For the primary outcome, there was a significant interaction between access site allocation (radial or femoral) and acute coronary syndrome type (STEMI or NSTEACS) with an interaction p value of 0.025. In patients with STEMI **(A)**, radial artery access reduced the primary outcome compared with femoral artery access, whereas in patients with NSTEACS **(B)**, there was no significant difference between radial and femoral artery access. CI = confidence interval; HR = hazard ratio; NSTEACS = non–ST-segment elevation acute coronary syndrome; STEMI = ST-segment elevation myocardial infarction.

with 5.2% of patients randomized to femoral access (HR: 0.60; 95% CI: 0.38 to 0.94; p = 0.026) (Fig. 1A, Table 3). Compared with femoral access, radial access also reduced the first secondary composite outcome of death, MI, or stroke (2.7% vs. 4.6%; HR: 0.59; 95% CI: 0.36 to 0.95; p = 0.031). This benefit was driven mainly by a reduction in mortality with radial artery access (1.3% vs. 3.2%; HR: 0.39; 95% CI: 0.20 to 0.76; p = 0.006), with similar rates of MI and stroke (Fig. 2A, Table 3). The other secondary outcome of non-CABG major bleeding occurred infrequently and was not significantly different between the groups (Table 3).

Among patients with NSTEACS, the primary outcome occurred in 3.8% randomized to radial artery intervention compared with 3.5% randomized to femoral artery intervention (HR: 1.11; 95% CI: 0.83 to 1.48; p = 0.49) (Fig. 1B, Table 3). There were no reductions in either of the 2 secondary outcomes or in any of the individual components of the primary outcome (Table 3). Moreover, among NSTEACS patients who underwent PCI, we found no significant difference in the primary outcome between the radial (3.63%, n = 1,486) and femoral (3.38%, n = 1,507) groups (HR: 1.07; 95% CI: 0.73 to 1.57; p = 0.73). In patients with unstable angina (n = 1,903; PCI rate: 53.9%), the primary outcome was 2.40% in the radial group and 2.65% in the femoral group (HR: 0.90; 95% CI: 0.51 to 1.59), and there was a reduction in ACUITY major bleeding (1.20% vs. 3.87%; HR: 0.31: 95% CI: 0.16 to 0.60). Similarly, in patients with non–ST-segment elevation myocardial infarction (n = 3,160; PCI rate: 62.2%) , the primary outcome was similar in the radial and femoral artery groups (4.76% radial vs. 3.92% femoral; HR: 1.21; 95% CI: 0.87 to 1.70) with a reduction in ACUITY major bleeding (2.26% vs. 4.80%; HR: 0.47; 95% CI: 0.31 to 0.70).

Other outcomes. PCI success rates were similar in the radial and femoral groups in both STEMI and NSTEACS patients. ACUITY major bleeding (defined as RIVAL major bleeding + large hematomas + pseudoaneurysms requiring closure) occurred less frequently in patients with STEMI allocated to radial artery access (HR: 0.49; 95% CI: 0.28 to 0.84; p = 0.009) as well as in patients with NSTEACS (HR: 0.41; 95% CI: 0.29 to 0.58; p < 0.0001), without significant heterogeneity (Table 3). Similarly, major vascular access site complications alone were reduced with radial access in both STEMI and NSTEACS, with no significant heterogeneity (Table 3). Access site crossover was higher in the radial group compared with the femoral group, and this was consistent in both STEMI and NSTEACS cohorts.

Primary PCI. Among patients with STEMI undergoing PCI, 1,451 patients (74%) received a primary PCI and 507 patients (26%) received a secondary PCI (i.e., 3% facilitated, 12% rescue, or 11% routine adjunctive). For the primary outcome, there was no heterogeneity in treatment effect in patients receiving a primary versus secondary PCI (interaction p = 0.79). Among patients undergoing primary PCI, 30-day mortality occurred in 1.4% of patients randomized to radial access versus 3.07% randomized to femoral access (HR: 0.46; 95% CI: 0.22 to 0.97; p = 0.041). Major vascular access site complications (1.4% vs. 4.0%; HR: 0.35; p = 0.005) and ACUITY-defined major bleeding (1.86% vs. 4.68%; HR: 0.39; p = 0.004) were substantially lower with radial access in primary PCI patients. Overall time from hospital presentation to PCI start was not significantly different between the radial and femoral access groups (Table 2). However, time from randomization to the end of PCI was 5 min longer in the radial artery group (58 min vs. 53 min, p = 0.0009).

Table 3 Efficacy and Safety Outcomes in Patients With STEMI and NSTEACS

	STEMI				NSTEACS				
	Radial (n = 955)	Femoral (n = 1,003)	HR (95% CI)	p Value	Radial (n = 2,552)	Femoral (n = 2,511)	HR (95% CI)	p Value	Interaction p Value
Death, MI, stroke or non-CABG major bleed (primary outcome)	30 (3.14)	52 (5.19)	0.60 (0.38–0.94)	0.026	98 (3.84)	87 (3.46)	1.11 (0.83–1.48)	0.491	0.025
Death, MI or stroke (secondary outcome)	26 (2.72)	46 (4.59)	0.59 (0.36–0.95)	0.031	86 (3.37)	68 (2.71)	1.25 (0.91–1.71)	0.176	0.011
Non-CABG major bleed (secondary outcome)	8 (0.84)	9 (0.91)	0.92 (0.36–2.39)	0.870	16 (0.63)	24 (0.96)	0.66 (0.35–1.23)	0.190	0.557
Access site related	1 (0.10)	2 (0.20)	0.53 (0.05–5.84)	0.604	4 (0.16)	10 (0.40)	0.39 (0.12–1.26)	0.116	0.838
Non–access site related	7 (0.74)	7 (0.71)	1.04 (0.36–2.95)	0.948	12 (0.47)	14 (0.56)	0.84 (0.39–1.82)	0.664	0.753
ACUITY major bleed	19 (1.99)	41 (4.10)	0.49 (0.28–0.84)	0.009	47 (1.84)	112 (4.46)	0.41 (0.29–0.58)	<0.001	0.624
Access site related	12 (1.26)	34 (3.39)	0.37(0.19–0.72)	0.003	36 (1.41)	98 (3.90)	0.36 (0.25–0.53)	<0.0001	0.955
Non–access site related	7 (0.74)	7 (0.71)	1.04 (0.36–2.95)	0.948	11 (0.43)	14 (0.56)	0.77 (0.35–1.70)	0.521	0.656
Death	12 (1.26)	32 (3.19)	0.39 (0.20–0.76)	0.006	32 (1.25)	19 (0.76)	1.66 (0.94–2.92)	0.082	0.001
MI	11 (1.16)	18 (1.82)	0.63 (0.30–-1.33)	0.225	49 (1.92)	47 (1.87)	1.03 (0.69–1.53)	0.903	0.269
Stroke	5 (0.53)	4 (0.40)	1.30 (0.35–4.84)	0.696	15 (0.59)	10 (0.40)	1.48 (0.67–3.30)	0.335	0.864
Major vascular access site complication	12 (1.26)	35 (3.49)	0.36 (0.19–0.70)	0.002	37 (1.45)	96 (3.82)	0.38 (0.26–0.55)	<0.001	0.885
PCI success*	789 (95.7)	806 (95.8)	1.00 (0.91–1.10)	1.000	1415 (95.3)	1429 (94.8)	1.01 (0.94–1.09)	0.813	0.924
Access site crossover	51 (5.34)	16 (1.60)	3.32 (1.89–5.82)	<0.001	214 (8.39)	54 (2.15)	3.94 (2.92–5.31)	<0.001	0.606
Minor bleed	33 (3.48)	22 (2.21)	1.59 (0.93–2.72)	0.093	67 (2.63)	96 (3.83)	0.68 (0.50–0.93)	0.016	0.008
TIMI major bleed	8 (0.84)	6 (0.61)	1.37 (0.48–3.96)	0.556	11 (0.43)	13 (0.52)	0.83 (0.37–1.86)	0.658	0.457
Any blood transfusion	11 (1.16)	15 (1.51)	0.76 (0.35–1.66)	0.493	88 (3.46)	83 (3.31)	1.05 (0.78–1.41)	0.765	0.446
Death, MI, stroke or ACUITY major bleed	40 (4.19)	82 (8.18)	0.51 (0.35–0.74)	<0.001	127 (4.98)	174 (6.93)	0.71 (0.56–0.89)	0.003	0.129
Stent thrombosis*	4 (0.49)	12 (1.44)	0.34 (0.11–1.07)	0.065	12 (0.81)	14 (0.93)	0.87 (0.40–1.87)	0.713	0.187
Definite stent thrombosis*	3 (0.37)	6 (0.72)	0.51 (0.13–2.04)	0.341	5 (0.34)	10 (0.66)	0.51 (0.17–1.48)	0.213	0.989
Probable stent thrombosis*	1 (0.12)	6 (0.72)	0.18 (0.02–1.45)	0.107	7 (0.47)	5 (0.33)	1.41 (0.45–4.44)	0.558	0.089

Values are n (%). *Among patients who had PCI: STEMI: 825 in the radial group and 842 in the femoral group. NSTEACS: 1,486 in then radial group and 1,507 in the femoral group.
CI = confidence interval; HR = hazard ratio; TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Tables 1 and 2.

Predictors of death. In a multivariable model for death, the interaction between pre-randomization diagnosis (STEMI vs. NSTEACS) and randomized treatment (radial vs. femoral access) remained highly significant (p = 0.0001), after adjustment for baseline variables, center radial volume, and operator radial experience (Table 4). Analyses focusing on bivalirudin revealed no significant interaction in the primary outcome between access site allocation and a bivalirudin-based anticoagulation strategy and one that did not include bivalirudin in the overall cohort of STEMI plus NSTEACS patients (p for interaction = 0.2823). Similarly, among patients with STEMI, there was also no significant interaction between a bivalirudin-based strategy and access site allocation (p for interaction = 0.5519).

Other independent predictors of death included older age, diabetes, current smoking, and PCI performed at a low- (compared with a high-) volume radial center.

Among patients with STEMI, those who died by day 30 were more likely to have experienced a major bleeding event compared with those who survived (11.0% vs. 1.0%, p < 0.0001) (Table 5). Other factors significantly associated with death included femoral artery access site allocation, older age, female sex, CABG surgery after randomization, unsuccessful PCI, stent thrombosis, and new MI (Table 5).

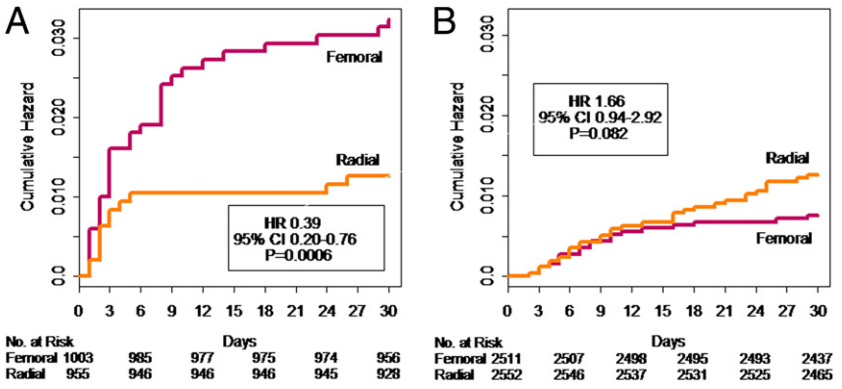

Figure 2 Death in Patients With STEMI and NSTEACS

For death, there was a significant interaction between access site allocation (radial or femoral) and acute coronary syndrome type (STEMI or NSTEACS) with an interaction p value of 0.001. In patients with STEMI **(A)**, radial artery access reduced the mortality compared with femoral artery access, whereas in patients with NSTEACS **(B)**, there was no significant difference in mortality between radial and femoral artery access. Abbreviations as in Figure 1.

Discussion

RIVAL is the largest randomized comparison of radial and femoral artery access in patients with STEMI as well as in those with NSTEACS. In patients with STEMI, radial artery access significantly reduced the primary outcome and the secondary outcome of death, MI, or stroke as well as all-cause mortality. In patients presenting with NSTEACS, we found no significant differences in any of these outcomes. In both STEMI and NSTEACS patients, radial access reduced major vascular access site complications and major bleeding as defined by the ACUITY definition.

In STEMI patients, the reduction in the primary and secondary composite outcomes was driven mainly by a reduction in mortality with a directionally consistent reduction in MI. No such benefit was observed in patients with NSTEACS. In the multivariable analysis, this interaction between pre-randomization ACS type and access-site allocation remained highly significant, even after adjustment for baseline variables, operator radial experience, and center radial volume. There are several plausible reasons why a differential response to radial versus femoral access on mortality might occur. First, within the first 30 days, STEMI patients are at higher risk of mortality compared

Table 4 Multivariable Predictors of Mortality in RIVAL

Variable	HR	95% CI	p Value
Access site (radial vs. femoral) in STEMI cohort	0.266	0.127–0.561	0.0005
Access site (radial vs. femoral) in NSTEACS cohort	1.680	0.951–2.965	0.0737
ACS type (STEMI vs. NSTEACS) in femoral group	5.364	2.972–9.682	<0.0001
ACS type (STEMI vs. NSTEACS) in radial group	0.851	0.400–1.812	0.6753
Access site × ACS type interaction	—	—	0.0001
Operator radial volume			
Tertile 2 vs. tertile 1	1.486	0.783–2.818	0.2256
Tertile 3 vs. tertile 1	1.508	0.722–3.149	0.2746
Center radial volume			
Tertile 2 vs. tertile 1	0.711	0.377–1.339	0.2906
Tertile 3 vs. tertile 1	0.524	0.243–1.129	0.0987
Age (per 1-yr increase)	1.086	1.061–1.111	<0.0001
Sex (men vs. women)	0.855	0.530–1.379	0.5212
Diabetes vs. no diabetes	1.862	1.188–2.919	0.0067
Previous MI vs. no previous MI	1.111	0.614–2.009	0.7274
Previous PCI vs. no previous PCI	0.631	0.281–1.414	0.2630
Smoker vs. non- or previous smoker	1.995	1.207–3.299	0.0071
PAD vs. no PAD	1.446	0.620–3.375	0.3935
Body mass index	0.970	0.923–1.019	0.2271
Baseline hemoglobin	0.895	0.791–1.013	0.0780

ACS = acute coronary syndromes; PAD = peripheral artery disease; other abbreviations as in Tables 1 and 3.

Table 5 Characteristics of STEMI Patients Who Died Versus Those Who Survived at Day 30

Characteristic	Overall (N = 1,958)	Patients Who Died (n = 44)	Patients Who Survived (n = 1,914)	p Value
Age, yrs	60 ± 12	64 ± 12	59 ± 12	<0.0001
Diabetes	345 (17.6)	12 (27.3)	333 (17.4)	0.0892
Previous PCI or CABG	129 (6.6)	2 (4.5)	127 (6.6)	0.5806
Female	410 (20.9)	16 (36.4)	394 (20.6)	0.0110
Access site randomization to radial	955 (48.8)	12 (27.3)	943 (49.3)	0.0039
Crossover from radial to femoral (yes)	51 (5.3)	2 (16.7)	49 (5.2)	0.0791
Access site randomization to femoral	1,003 (51.2)	32 (72.7)	971 (50.7)	0.0039
Crossover from femoral to radial (yes)	16 (1.6)	0 (0.0)	16 (1.6)	—
Non-CABG major bleed	17 (0.9)	4 (9.1)	13 (0.7)	<0.0001
Any major bleed	25 (1.3)	5 (11.4)	20 (1.0)	<0.0001
Non-CABG blood transfusion	13 (0.7)	2 (4.5)	11 (0.6)	0.0013
Minor bleed*	55 (2.8)	1 (2.3)	54 (2.8)	0.8276
CABG surgery after randomization	56 (2.9)	4 (9.1)	52 (2.7)	0.0121
Vascular access complication	47 (2.4)	0 (0.0)	47 (2.5)	—
ACUITY major bleed	60 (3.1)	4 (9.1)	56 (2.9)	0.0190
Non-CABG ACUITY major bleed	Same			
PCI success*	1,595 (95.7)	25 (78.1)	1,570 (96.0)	<0.0001
Stent thrombosis (definite or probable)*	16 (1.0)	8 (25.0)	8 (0.5)	<0.0001
MI after randomization	29 (1.5)	4 (9.1)	25 (1.3)	<0.0001
Stroke after randomization	9 (0.5)	4 (9.1)	5 (0.3)	<0.0001

Values are mean ± SD or n (%). *Among patients who had PCI: 32 died, 1,635 survived.
Abbreviations as in Tables 1 and 2.

with NSTEACS patients (3.19% vs. 0.76%, respectively in the femoral access site groups), in whom nonfatal ischemic events (i.e., new MI) are more common (21,22). Therefore, if a reduction in bleeding-related complications was associated with lower mortality, it might most likely be detected in the STEMI group of patients. Second, STEMI patients generally undergo a much higher rate of PCIs (>90%) compared with NSTEACS patients (50% to 60%), exposing them to a higher frequency of access site complications. Third, STEMI patients are often treated with more potent initial and subsequent antiplatelet and antithrombotic therapies (as well as fibrinolytic therapy) compared with patients with NSTEACS. Therefore, the risk-adjusted rate of bleeding (particularly access-site bleeding) is higher, making the association between bleeding and mortality more readily detectable in this population.

In RIVAL, we observed substantially lower rates of major vascular access site complications and ACUITY-defined bleeding with radial access in both the STEMI and NSTEACS cohorts. The rate of bleeding using the more conservative RIVAL study definition, which excluded major vascular access site complications (unless they led to death, hemoglobin decrease of 5 g/dl, blood transfusion of >2 units, or surgery), was very low (<1%), and consequently no difference was found between the 2 groups. Despite this, we found much higher 30-day mortality rates among those patients who had a non-CABG–related major bleeding event compared with those who did not in both the STEMI and NSTEACS populations, irrespective of whether the RIVAL or ACUITY bleeding definition was used. One possibility is that in the STEMI population, operators were significantly more experienced, as were centers in the performance of transradial intervention, compared with the NSTEACS population. There is clearly a learning curve for radial artery intervention, and there may be a threshold before significant benefits with this procedure are observed. Despite this, in a multivariable model of predictors of mortality in RIVAL, the interaction between pre-randomization ACS type and access site allocation remained highly significant, even after adjustment for baseline variables, operator and center experience, indicating that it was independent of operator and center radial access experience.

Our study has several strengths. It is the largest randomized comparison of radial and femoral access site approaches in patients with STEMI. The trial consisted of experienced operators and high-volume radial access site centers. Because RIVAL included both STEMI and NSTEACS patients in large numbers, it allowed us to compare and contrast the relative benefits and risks of radial intervention in these patients and explore reasons for a possible differential response.

Study limitations. Limitations of our analysis also need to be considered. The overall result of RIVAL on the primary outcome was neutral, so it may not be appropriate to look at subgroups because the overall result of the trial may be the most reliable (23,24). Replication in independent randomized trials would strengthen the conclusions of our analysis. In the RIFLE-ACS (Radial Versus Femoral Investigation in ST Elevation Acute Coronary Syndrome) trial of 1,001 patients with STEMI randomized to radial or femoral intervention, rates of bleeding due to access site complications (12.2% vs. 7.8%, p = 0.026) and subsequent mortality (9.2% vs. 5.2%, p = 0.020) were lower using the radial artery approach (27). Data from this independent study are

consistent with the results of the larger STEMI population in RIVAL. Second, there were exceedingly few RIVAL-defined major bleeding events in this trial (<1%). Although we demonstrated a much higher mortality rate in patients who experienced a major bleed compared with those who did not, the low frequency of events may have impeded our ability to determine whether a reduction in major bleeding could have affected longer-term mortality. Bleeding is an outcome that is definition dependent (25,26). Using the ACUITY definition of major bleeding, there were substantial reductions in bleeding in both the STEMI and NSTEACS cohorts in RIVAL. Third, because centers participating in RIVAL were highly experienced in the radial technique, similar outcomes may not apply in centers performing lower volumes. Fourth, the ACUITY definition of major bleeding used in RIVAL included large hematoma (defined as large if it prolonged hospitalization), which differs slightly from the ACUITY definition of hematoma (>5 cm). Finally, unfractionated heparin was the anticoagulation strategy most commonly used in RIVAL, with few patients receiving bivalirudin. However, in the HORIZON-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction Trial), there was a consistent benefit of the radial technique in patients receiving bivalirudin as well as those receiving heparin plus glycoprotein IIb/IIIa inhibitors (28).

Conclusions

In this large randomized comparison, radial artery access reduced the primary outcome and mortality in patients presenting with STEMI. There was no such benefit in patients presenting with NSTEACS. This interaction between ACS type and access site allocation was independent of operator radial experience and center radial volume. These data suggest that radial artery access might be the preferred option in patients with STEMI.

Reprint requests and correspondence: Dr. Shamir R. Mehta, Hamilton Health Sciences, General Division, David Braley Cardiac, Vascular and Stroke Institute, Room C3-119, 237 Barton Street East, Hamilton, Ontario L8L 2X2, Canada. E-mail: smehta@mcmaster.ca.

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Key Words: bleeding ■ percutaneous coronary intervention ■ radial artery ■ ST-segment elevation myocardial infarction ■ vascular access.