ORIGINAL RESEARCH

Relationship Between Arterial Access and Outcomes in ST-Elevation Myocardial Infarction With a Pharmacoinvasive Versus Primary Percutaneous Coronary Intervention Strategy: Insights From the STrategic Reperfusion Early After Myocardial Infarction (STREAM) Study

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***Background*—**The effectiveness of radial access (RA) in ST-elevation myocardial infarction (STEMI) has been predominantly established in primary percutaneous coronary intervention (pPCI) with limited exploration of this issue in the early postfibrinolytic patient. The purpose of this study was to compare the effectiveness and safety of RA versus femoral (FA) access in STEMI undergoing either a pharmacoinvasive (PI) strategy or pPCI.

***Methods and Results*—**Within STrategic Reperfusion Early After Myocardial Infarction (STREAM), we evaluated the relationship between arterial access site and primary outcome (30-day composite of death, shock, congestive heart failure, or reinfarction) and major bleeding according to the treatment strategy received. A total of 1820 STEMI patients were included: 895 PI (49.2%; rescue PCI [n=379; 42.3%], scheduled PCI [n=516; 57.7%]) and 925 pPCI (50.8%). Irrespective of treatment strategy, there was comparable utilization of either access site (FA: PI 53.4% and pPCI 57.6%). FA STEMI patients were younger, had lower presenting systolic blood pressure, lesser Thrombolysis In Myocardial Infarction risk, and more ∑ST-elevation at baseline. The primary composite endpoint occurred in 8.9% RA versus 15.7% FA patients ($P<0.001$). On multivariable analysis, this benefit on the primary composite outcome favoring RA persisted (adjusted odds ratio [OR], 0.59; 95% CI, 0.44–0.78; $P<0.001$) and was evident in both pPCI (adjusted OR, 0.63; 95% CI, 0.43–0.92) and PI cohorts (adjusted OR, 0.57 95% CI, 0.37–0.86; P interaction=0.730). There was no difference in nonintracranial major bleeding with either access group (RA vs FA, 5.2% vs 6.0%; $P=0.489$).

***Conclusions*—**Regardless of the application of a PI or pPCI strategy, RA was associated with improved clinical outcomes, supporting current STEMI evidence in favor of RA in PCI.

***Clinical Trial Registration*—**URL: https://www.clinicaltrials.gov/. Unique identifier: NCT00623623. **(*J Am Heart Assoc*. 2016;5: e003559 doi: 10.1161/JAHA.116.003559)**

Key Words: arterial access • pharmacoinvasive strategy • primary percutaneous coronary intervention • ST-segment elevation myocardial infarction

The utilization of radial (RA) over femoral arterial access (FA) for acute coronary intervention in ST-elevation myocardial infarction (STEMI) is supported by a reduction in mortality, ischemic, and bleeding endpoints.[1–8] This has led various interventional societies to encourage its utilization over femoral access.[9–11] Although the basis of this evidence

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*Accompanying Tables S1, S2, and Appendix S1 (which lists the participating STREAM Investigators and countries) are available at http://jaha.ahajournals.org/content/5/6/e003559/DC1/embed/inline-supplementarymaterial-1.pdf

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includes patients undergoing both primary and rescue percutaneous coronary intervention (PCI), the majority of randomized data are confined to patients treated with primary PCI (pPCI).[2,7] RA in patients treated with a fibrinolytic pharmacoinvasive strategy (PI) has had limited exploration,[12–14] as has any direct comparison with patients treated with pPCI. Moreover, the application of a PI strategy creates at least 2 distinct patient subsets at the time of angiography, each with a different risk profile with respect to ischemic outcomes and major bleeding/access-site complications.[15] The first is the "nonreperfused" patient requiring urgent rescue PCI who has received recent fibrinolysis with adjunctive antithrombotic and antiplatelet therapy sometimes associated with hemodynamic or electrical instability. The second is the stable "reperfused" STEMI undergoing scheduled PCI 6 to 24 hours later. Intuitively, a comparable efficacy and safety advantage —as observed in pPCI in favor of RA—is expected in patients treated with a PI strategy, particularly in the subset undergoing rescue PCI.

The STrategic Reperfusion Early After Myocardial infarction (STREAM) trial,[16] which randomized patients to a fibrinolytic PI (rescue and scheduled PCI) versus pPCI treatment strategy, provided a unique opportunity to address this issue in an early presenting, rapidly treated contemporary STEMI cohort. Accordingly, within STREAM, we evaluated the relationship between arterial access site and the 30-day primary composite (all cause death, shock, congestive heart failure [CHF], and reinfarction) as well as major bleeding events in STEMI according to the treatment strategy received.

Methods

Study Design and Patient Population

The STREAM trial protocol and primary results have been published previously.[16,17] The study protocol was approved by national regulatory authorities and by the local ethics committee at each study center. All patients provided written informed consent. In brief, acute STEMI patients presenting within 3 hours of symptom onset and unable to undergo pPCI within 1 hour of first medical contact were randomized to either fibrinolysis with a protocol-defined PI strategy or pPCI. In the PI strategy, bolus weight-based tenecteplase (TNK), aspirin, clopidogrel, and enoxaparin were administered according to guideline recommendations and followed by either rescue PCI or scheduled angiography (within 6–24 hours). After 21% of the ultimate population had been enrolled, the executive committee amended the protocol on August 24, 2009, to reduce the dose of TNK by 50% in patients 75 years of age or older because of an excess of intracranial hemorrhage (ICH) in that age group. The need for rescue PCI was determined by site investigators according to <50% ST segment resolution in the electrocardiogram (ECG) lead with the maximal ST-elevation 90 minutes after TNK bolus, hemodynamic instability, or refractory ventricular arrhythmias as mandated by the study protocol. Primary PCI was conducted after expeditious transfer from the point of randomization, and early initiation of aspirin, clopidogrel, and antithrombotic therapy, including discretionary glycoprotein IIb/IIIa (GP 2b/3a) antagonists based on best standard practice.

ECGs were performed at baseline, 90 minutes post-TNK, and 30 minutes postcatheterization in the pharmacoinvasive arm (including post-PCI in those undergoing PCI) and baseline and 30 minutes postcatheterization or post-PCI (if performed) in the primary PCI arm. Interpretation was performed at the Canadian VIGOUR Center ECG Core Laboratory (Edmonton, Alberta, Canada), and, for this study, the prespecified ECG metrics included: worst lead ST-elevation resolution; worst lead ST-elevation resolution ≥50%; and worst lead residual ST-elevation. Both worst lead ST-elevation resolution and worst lead residual ST-elevation have previously been shown to have prognostic utility in STEMI patients undergoing primary PCI.[18]

Interventional cardiologists in participating sites determined the choice of the arterial access, either RA or FA based upon local practice (Table S1). Angiographic assessment detailing coronary anatomy, need for percutaneous intervention after diagnostic angiography and Thrombolysis In Myocardial Infarction (TIMI) flow grade post-PCI was performed locally by site-specific investigators using standard definitions.[19] Management of the arterial sheath postangiography was also determined by site-specific vascular access best practice protocols. The results of the current report are based on the per-protocol analysis according to the access site utilized to complete the angiographic procedure.

The primary outcome of this study was a 30-day composite of death, cardiogenic shock, CHF, or reinfarction whereas the key secondary outcomes included components of the primary outcome at 30 days, nonintracranial major bleeding or ICH, stroke, and 1-year all-cause mortality.

Detailed definitions for both the components of the primary composite and bleeding endpoints have been published previously.[17] Briefly, a stroke review independent panel adjudicated all strokes centrally. The Global Use of Strategies to Open Occluded Arteries (GUSTO) definition of bleeding[20] was implemented in this trial. Major bleeding was classified as: (1) intracranial or (2) nonintracranial—severe bleed (bleed that leads to hemodynamic compromise requiring intervention [blood or fluid replacement, inotropic support, ventricular assist device, or surgical repair] or life-threatening or fatal bleed) or moderate bleed (bleeding requiring blood transfusion, but that does not lead to hemodynamic compromise requiring intervention). All bleeds, excluding intracranial bleeds, were investigator reported. Access-site–related major bleeding was defined as major bleeding that occurred less

than 48 hours post-PCI. Major access-site vascular complication included development of a pseudoaneurysm or an arteriovenous fistula.

Statistical Analysis

Categorical variables are summarized as percentages and as median (25th, 75th percentiles) for continuous variables. Baseline characteristics and concomitant treatment are reported according to access site (radial vs femoral) and study treatment received. Differences between groups were tested with the chi-square test (or Fisher's exact test when count was <5 for at least 1 cell) for categorical variables and Wilcoxon rank-sum test for continuous variables, respectively.

The association between access site and primary clinical outcome (composite of death, cardiogenic shock, CHF, or reinfarction) within 30 days was examined using a univariable logistic regression model where a propensity score for access site was used to construct an inverse probability weight.[21] Given the assignment of access site was not randomized, a propensity score for access site was created using a multivariable logistic regression model. Variables considered in the model were based on literature review, expert opinion, and univariate tests with $P<0.10$. The covariates in the final model were forced in; that is, no conventional statistical selection techniques (eg, stepwise, forward, or backward) were used. Variables included in the final propensity score model were age, sex, weight, history of hypertension, history of diabetes mellitus, heart rate, systolic blood pressure, Killip class, inferior myocardial infarction (MI), sum ST elevation at baseline, Q waves at baseline, time from symptom onset to randomization, and country of enrollment (Table S2). The interaction between access site and study treatment (ie, PI vs pPCI) on the 30-day primary clinical composite outcome was also examined. A further prespecified similar subgroup analysis of access site within the PI (rescue vs scheduled) strategy was performed.

To test whether GP 2b/3a use and protocol amendment modulate the association between access site and 30-day primary outcomes, the interaction between GP 2b/3a use and access site and the interaction between protocol amendment and access site were examined. Odds ratios (ORs) with 95% CIs are reported. All statistical tests were 2-sided, with $P<0.05$ considered as statistically significant. Statistical analyses were performed using SAS software (version 9.4; SAS Institute Inc., Cary, NC).

Results

Baseline Characteristics

Figure 1 illustrates the 2 treatment group cohorts from the 1820 per-protocol treated patients enrolled in STREAM categorized by access site. As evident, there was comparable utilization of either access site within each treatment strategy (FA: PI 53.4% [n=478] and pPCI 57.6% [n=533]). In addition, within the PI strategy, both access sites were comparably distributed in the rescue (FA: 52.8%; n=200) and scheduled PCI (FA: 53.9%; n=278) subgroups.

Overall, STEMI patients treated by FA were younger, had more past hypertension, lower systolic BP at presentation, lower TIMI Risk Score, and more ST-elevation on the baseline

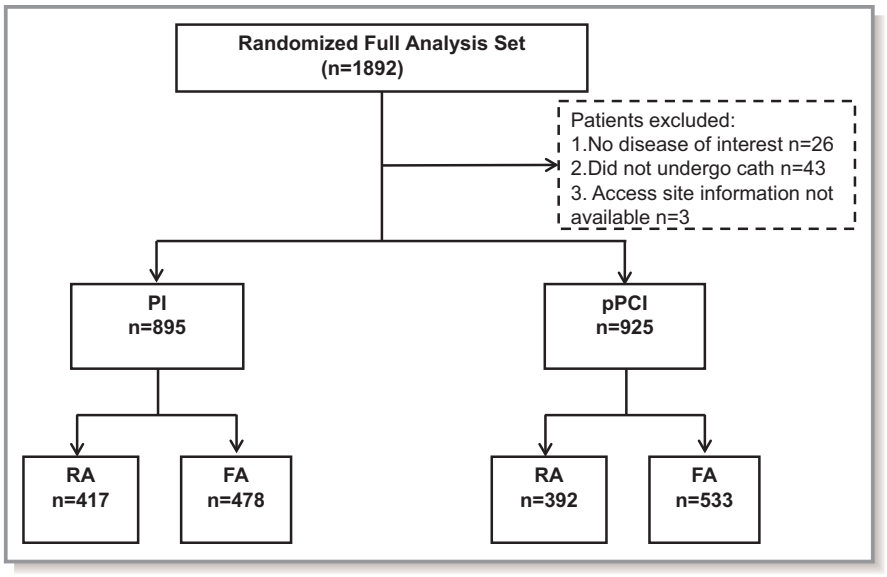

Figure 1. Study patients' flow chart. FA indicates femoral; PI, pharmacoinvasive; pPCI, primary percutaneous coronary intervention; RA, radial.

ECG compared to the RA group (Table 1). These findings were consistent within both PI and pPCI patients.

As described in Table 2, patients treated by FA had shorter time from symptom onset to randomization in both treatment strategies. In addition, shorter times from symptom onset to femoral, compared to radial sheath, insertion were observed in the pPCI, but not in the PI, strategy.

A significantly higher utilization of GP2b/3a inhibitor use was noted in the RA, compared to FA, group (40.2% vs 24.1%; $P<0.001$), particularly in those undergoing pPCI. Those patients treated with pPCI strategy and RA had higher rates of post-PCI TIMI-3 flow grade than FA patients. Evaluation of the post-treatment ECG revealed consistently better indices of reperfusion for patients with RA in both the PI and pPCI cohorts, as evidenced by higher rates of worst lead residual ST elevation <1 mm and lesser rates in patients with ≥2 mm residual ST elevation.

Primary Outcome

Irrespective of treatment strategy, the unadjusted primary composite of 30-day death, shock, CHF, or reinfarction occurred in 8.9% in the RA compared to 15.7% in FA group (Table 3). After adjustment, the benefit favoring RA persisted (adjusted OR, 0.59; 95% CI, 0.44–0.78; $P<0.001$), as seen in Figure 2.

Analysis of access site categorized by study treatment received revealed that the advantage associated with RA was present in both the pPCI (adjusted OR, 0.63; 95% CI, 0.43–0.92) and PI cohorts (adjusted OR, 0.57; 95% CI, 0.37–0.86; P [interaction]=0.730; Figure 2). Within the PI group, a trend for RA advantage was evident in the high-risk rescue PCI (13.4% vs 26.3%; adjusted OR, 0.65; 95% CI, 0.39–1.07) subgroup with no significant difference in patients undergoing scheduled PCI (5.5% vs 5.4%; adjusted

Table 1. Selected Baseline Patient Characteristics According to Access Site and Study Treatment

	All			PI			pPCI		
	RA	FA	*P* Value	RA	FA	*P* Value	RA	FA	*P* Value
N	809	1011		417	478		392	533	
Age, y	60 (52, 71)	58 (50, 66)	<0.001	60 (52, 71)	58 (50, 65)	0.001	60 (52, 70)	58 (51, 66)	0.024
Female sex, n (%)	161 (19.9)	214 (21.2)	0.507	80 (19.2)	93 (19.5)	0.918	81 (20.7)	121 (22.7)	0.458
Hypertension, n (%)	343 (42.8)	472 (47.7)	0.038	188 (45.4)	227 (48.5)	0.358	155 (39.9)	245 (46.9)	0.036
Diabetes mellitus, n (%)	99 (12.3)	129 (12.9)	0.698	52 (12.5)	58 (12.3)	0.923	47 (12.1)	71 (13.5)	0.535
Heart rate, bpm	73 (63, 84)	75 (62, 86)	0.434	73 (61, 85)	75 (62, 86)	0.147	75 (65, 83)	75 (62, 85)	0.670
Systolic blood pressure, mm Hg	139 (122, 156)	130 (120, 150)	<0.001	138 (122, 152)	130 (120, 150)	0.002	140 (123, 157)	134 (120, 150)	0.004
Killip class >I, n (%)	49 (6.2)	49 (5.3)	0.402	27 (6.6)	25 (5.7)	0.600	22 (5.8)	24 (4.9)	0.541
TIMI Risk Score ≥5, n (%)	120 (15.4)	97 (10.8)	0.005	61 (15.1)	44 (10.5)	0.048	59 (15.8)	53 (11.1)	0.045
Inferior MI*, n (%)	402 (50.2)	506 (50.7)	0.845	212 (50.8)	230 (48.9)	0.572	190 (49.5)	276 (52.2)	0.421
Baseline STE at worst lead*, mm	3 (2, 4)	3 (2, 4)	0.029	3 (2, 4)	3 (2, 5)	0.194	3 (2, 4)	3 (2, 4)	0.063
Q wave in the infarct territory at baseline*, n (%)	251 (31.6)	325 (32.7)	0.624	132 (32.0)	154 (32.8)	0.782	119 (31.2)	171 (32.5)	0.665

Continuous variables presented as median (25th–75th percentiles). FA indicates femoral; MI, myocardial infarction; pPCI, primary percutaneous coronary intervention; RA, radial; STE, ST-segment elevation; TIMI, Thrombolysis In Myocardial Infarction.
*Evaluated by ECG Core Laboratory at the Canadian VIGOUR Centre.

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Table 2. Ischemic Times, Medications, Angiographic Findings, and Post-Treatment ECG According to Access Site and Study Treatment

	All			PI			pPCI		
	RA	FA	*P* Value	RA	FA	*P* Value	RA	FA	*P* Value
N	809	1011		417	478		392	533	
Ischemic times									
Symptom onset to randomization, min	96 (69, 140)	88 (63, 126)	<0.001	95 (68, 142)	89 (65, 124)	0.012	97 (70, 138)	88 (61, 127)	0.007
Symptom onset to TNK, min	—	—	—	105 (79, 150)	97 (74, 135)	0.001	—	—	—
Symptom onset to sheath insertion, min	—	—	—	624 (260, 1320)	616 (268, 1218)	0.296	185 (153, 240)	170 (125, 225)	0.001
Medications									
GP 2b/3a given, n (%)	325 (40.2)	244 (24.1)	<0.001	44 (10.6)	36 (7.5)	0.114	281 (71.7)	208 (39.0)	<0.001
Clopidogrel given, n (%)	713 (88.4)	949 (94.4)	<0.001	362 (87.2)	451 (95.6)	<0.001	351 (89.5)	498 (93.4)	0.033
Unfractionated heparin, n (%)	525 (64.9)	517 (51.1)	<0.001	242 (58.0)	115 (24.1)	<0.001	283 (72.2)	402 (75.4)	0.268
Angiographic									
Multivessel disease, n (%)	358 (46.3)	452 (46.7)	0.874	184 (46.2)	226 (48.7)	0.468	174 (46.4)	226 (44.8)	0.646
Patients receiving PCI, n (%)	689 (85.2)	885 (87.5)	0.142	341 (81.8)	385 (80.5)	0.639	348 (88.8)	500 (93.8)	0.006
Post-PCI TIMI Flow Grade, n (%)			0.121			0.495			0.036
0/1	16 (2.4)	27 (3.1)		11 (3.3)	9 (2.4)		5 (1.5)	18 (3.7)	
2	20 (3.0)	41 (4.8)		12 (3.6)	19 (5.1)		8 (2.3)	22 (4.5)	
3	640 (94.7)	791 (92.1)		310 (93.1)	342 (92.4)		330 (96.2)	449 (91.8)	
Post-treatment ECG*									
Worst-lead ST-elevation resolution, %	75 (50, 100)	71 (50, 100)	0.472	67 (33, 100)	67 (33, 100)	0.486	78 (57, 100)	75 (50, 100)	0.032
Worst-lead ST-elevation resolution ≥50%, n (%)	642 (86.8)	769 (83.7)	0.080	333 (87.4)	370 (87.5)	0.977	309 (86.1)	399 (80.4)	0.031
Worst-lead residual ST-elevation, n (%)			<0.001			0.019			0.001
<1 mm	364 (48.3)	355 (38.2)		205 (53.4)	188 (43.9)		159 (43.0)	167 (33.3)	
1 to <2 mm	267 (35.4)	350 (37.7)		127 (33.1)	161 (37.6)		140 (37.8)	189 (37.7)	
≥2 mm	123 (16.3)	224 (24.1)		52 (13.5)	79 (18.5)		71 (19.2)	145 (28.9)	

Continuous variables presented as median (25th–75th percentiles). *P* for comparison between RA and FA groups. ECG indicates electrocardiogram; FA, femoral; GP, glycoprotein; IABP, intra-aortic balloon pump; pPCI, primary percutaneous coronary intervention; RA, radial; TIMI, Thrombolysis In Myocardial Infarction; TNK, tenecteplase.

*Evaluated by ECG Core Laboratory at the Canadian VIGOUR Center.

Table 3. Efficacy and Safety Outcomes According to Access Site and Study Treatment

	All			PI			pPCI		
	RA	FA	*P* Value	RA	FA	*P* Value	RA	FA	*P* Value
N	809	1011		417	478		392	533	
30 days									
Primary composite endpoint: death/CHF/shock/reinfarction, n (%)	72 (8.9)	158 (15.7)	<0.001	37 (8.9)	67 (14.1)	0.016	35 (9.0)	91 (17.2)	<0.001
All-cause death, n (%)	19 (2.4)	47 (4.7)	0.009	9 (2.2)	23 (4.8)	0.032	10 (2.6)	24 (4.5)	0.119
Cardiogenic shock, n (%)	23 (2.9)	64 (6.4)	0.001	11 (2.6)	27 (5.7)	0.025	12 (3.1)	37 (7.0)	0.009
CHF, n (%)	40 (5.0)	84 (8.4)	0.005	19 (4.6)	36 (7.6)	0.062	21 (5.4)	48 (9.1)	0.037
Reinfarction, n (%)	15 (1.9)	26 (2.6)	0.302	11 (2.6)	10 (2.1)	0.600	4 (1.0)	16 (3.0)	0.041
Total strokes, n (%)	9 (1.1)	7 (0.7)	0.342	6 (1.4)	5 (1.1)	0.599	3 (0.8)	2 (0.4)	0.424
Intracranial hemorrhage, n (%)	5 (0.6)	2 (0.2)	0.150	4 (1.0)	2 (0.4)	0.323	1 (0.3)	0 (0.0)	0.243
Nonintracranial bleeding, major, n (%)	42 (5.2)	60 (6.0)	0.489	23 (5.5)	37 (7.8)	0.179	19 (4.9)	23 (4.3)	0.698
Access-site–related major bleeding, n (%)	23 (2.8)	41 (4.1)	0.163	12 (2.9)	23 (4.8)	0.137	11 (2.8)	18 (3.4)	0.622
1 year									
All-cause death, n (%)	37 (4.6)	63 (6.3)	0.125	21 (5.1)	30 (6.3)	0.418	16 (4.1)	33 (6.2)	0.163

CHF indicates congestive heart failure; pPCI, primary percutaneous coronary intervention.

OR, 0.55; 95% CI, 0.24–1.26). However, no interaction was evident between rescue PCI or scheduled PCI as it relates to the advantage of RA after adjustment (*P* [interaction]=0.739).

The observed increase in GP 2b/3a use within the RA group did not appear to modulate the association with the 30-day primary composite outcome (RA: GP 2b/3a use vs not, 9.3% versus 8.7%; and FA: 20.2% vs 14.3%; *P* [interaction] =0.988); neither did the implementation of the amendment (half-dose lytic in patients ≥75 years) of the STREAM trial protocol (RA and FA: pre- and postamendment, respectively, 9.0% vs 8.9% and 18.4% vs 15.2%; *P* [interaction]=0.920). The increased GP 2b/3a use within the RA group also did not appear to modulate the association with major bleeding (RA vs FA: adjusted hazard ratio, 0.56; 95% CI, 0.28–1.12; *P* [interaction]=0.087).

Secondary Outcomes

Radial access was associated with an observed reduction in 30-day mortality (2.4% vs 4.7%; *P*=0.009), cardiogenic shock (2.9% vs 6.4%; *P*=0.001), and heart failure (5.0% vs 8.4%; *P*=0.005; Table 3). No significant differences in ischemic stroke or ICH were noted in either vascular access site across the 2 treatment groups. At 1 year, no difference in all-cause mortality was noted in either access-site category across both study treatment groups.

Major Bleeding

Overall, a comparable rate of nonintracranial major bleeding was noted in the RA versus FA group (5.2% vs 6.0%; *P*=0.489; Table 3). This was also evident within the 2 treatment strategies (PI and pPCI: RA vs FA, 5.5% vs 7.8% [*P*=0.179] and 4.9% vs 4.3% [*P*=0.698], respectively); however, within the PI strategy, a trend to increased nonintracranial major bleeding in patients treated by FA within the rescue, compared to the scheduled, subgroup was observed (rescue and scheduled: RA vs FA, 6.1% vs 11.6% [*P*=0.064] and 5.1% vs 5.1% [*P*=0.996]). Both major access-site (RA vs FA, 2.8% vs 4.1%; *P*=0.163) and non-access-site (RA vs FA, 2.3% vs 1.9%; *P*=0.487) bleeding were similarly distributed in the overall study population. Major vascular access complication (pseudoaneurysm or arteriovenous fistula development) occurred in 0% in the RA and 1.4% in the FA group.

Discussion

The results of this study indicate that in early presenting STEMI (<3 hours from symptom onset), utilization of RA over FA is associated with a significant reduction in the composite of major adverse cardiovascular events regardless of the application of a fibrinolytic PI or pPCI strategy. In addition, within the PI strategy, the prognostic advantage of RA applies particularly to the higher risk rescue PCI cohort in whom a doubling of

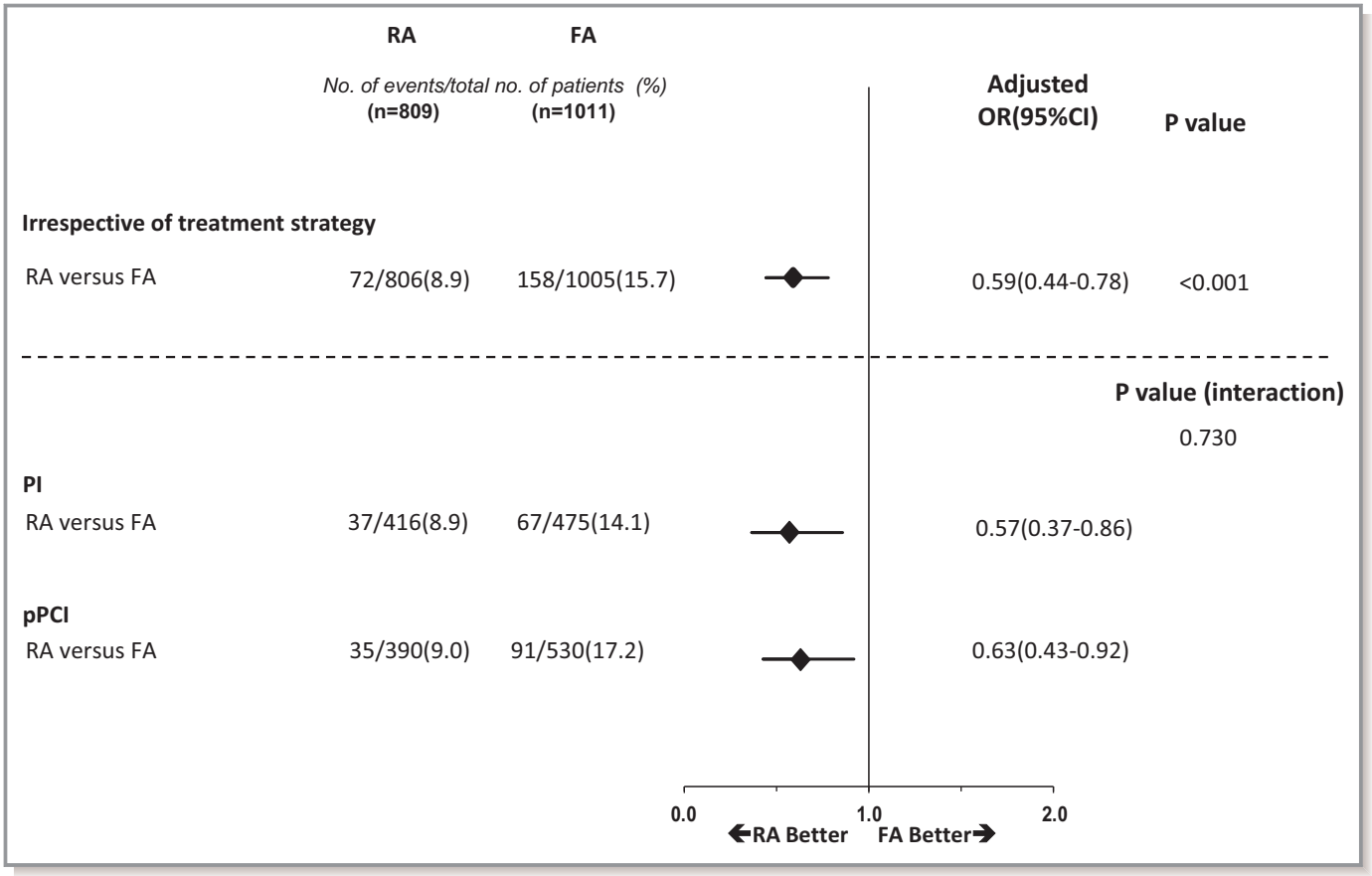

Figure 2. Upper panel: association between access site and primary endpoints irrespective of treatment strategy. Lower panel: association between access site and primary endpoints according to treatment strategy. Odds ratio (OR) was propensity score adjusted as an inverse probability weight. FA indicates femoral; PI, pharmacoinvasive; pPCI, primary percutaneous coronary intervention; RA, radial.

adverse outcomes appeared evident within the femoral access subgroup.

Within the STREAM study at baseline, patients treated by FA were more hypotensive and had greater ST elevation at presentation, reflective of adverse outcomes. Given this clinical profile, it is reasonable to suppose that this may have influenced the choice of FA and subsequently be reflected in worse outcomes. However, even after adjustment, the RA 30-day composite clinical outcomes and mortality advantage persisted.

The STREAM study enrolled patients presenting within 3 hours of symptom onset and thus represents a very early presenting STEMI population as compared to other trials that randomized access site in STEMI patients (12–24 hours).[2,3,7] Hence, this study evaluated a distinct STEMI cohort undergoing early cardiac catheterizations (except for scheduled PCI cohort) in the presence of potent antiantithrombotic and fibrinolytic agents. It would therefore seem that lower major bleeding would be associated with the observed significant reduction in the primary composite and 30-day mortality favoring RA across both treatment strategies. Although there was nominally less nonintracranial major access-site and non-access-site bleeding in those pharmacoinvasive-treated patients undergoing RA, this was not statistically significant. Apart from lower major bleeding, the mechanism by which radial access might relate to all-cause mortality currently remains unclear in the existing literature.[13,22] One plausible explanation for the observed prognostic difference favoring RA relates to selection bias introduced by operator experience and center-specific differences. Greater radial interventional expertise in high-volume centers may have been associated with improved outcomes resulting from reduced vascular complications.

To provide some context, it is noteworthy that 50% of the patients analyzed in the current study were treated with a fibrinolytic PI strategy, as compared to a much lower incidence in the Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome (RIFLE STEACS; 7.6% failed fibrinolysis)[2] and Radial versus femoral access for coronary intervention (RIVAL; 12%)[7] trials. Hence, the current results not only support the effectiveness of RA within a PI-treated STEMI patient subset, but also allow comparison of outcomes between roughly equal-sized groups undergoing different reperfusion strategies.

Compared to randomized trials that enrolled postfibrinolytic patients,[2,7] a higher proportion of major overall and

major access-site bleeding was noted in the current study; for instance, radial versus femoral, respectively, in RIVAL,[7] non–coronary artery bypass graft major bleeding (RIVAL definition) was noted in 0.84% versus 0.91%, whereas in RIFLE-STEACS (TIMI definition) 1.8% versus 2.8% compared to 5.2% and 6.0% in our study. The reasons for this disparity in major bleeding is unclear, but could relate to: (1) investigator—rather than central adjudication—of major bleeding in the current study; (2) heterogeneity in definition of major bleeding; (3) differences in the proportion of the postfibrinolytic STEMI population; and (4) variability in operator expertise and site-specific vascular access protocols. Despite no difference in nonintracranial major bleeding between the 2 access sites in this study, our adjusted analysis of 30-day mortality showed a persisting benefit associated with the radial approach. It is noteworthy that a recent study from the National Cardiovascular Data Registry's CathPCI Registry on bleeding complications in fibrinolytic-treated patients undergoing rescue PCI reported a major bleeding rate of 6.9% in radial versus 12.0% femoral access patients (adjusted OR, 0.67; 95% CI, 0.52–0.87; P=0.003).[23] RA was employed in only 16% of these patients, and the authors highlighted the need for further data in this "understudied high-risk group."

Our study has both limitations and strengths. Given that the choice of vascular access site was left to investigator discretion and absence of access to detailed procedural elements, we cannot exclude the impact of unmeasured confounders. Additionally, selection bias introduced by absence of information on center- and operator-specific interventional volumes cannot be excluded. Although we found no overall difference in vascular access bleeding, the trend toward more FA access bleeding in the PI patients undergoing rescue PCI suggests less bleeding hazard in the presence of recent fibrinolytic treatment when radial access is employed. STREAM excluded patients in cardiogenic shock and advanced kidney disease: Hence, our findings do not apply to this population. Given that STREAM was an open-label trial without central adjudication of bleeding endpoints, investigator bias may have played a role in the disparity in bleeding rates between this study and existing literature.

However, to the best of our knowledge, it is the largest data set comparing a randomized, multicenter fibrinolytic PI strategy (rescue and scheduled PCI) in a very early-treated STEMI population to pPCI, demonstrating that the outcomes advantage with RA occurs in both the PI and pPCI strategy.

Conclusion

Irrespective of whether a pPCI or PI reperfusion strategy is used, these results support the utilization of radial access as the preferred arterial access site in STEMI.

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SUPPLEMENTAL MATERIAL

Table S1. Radial vs. Femoral access according to country of enrollment.

Country	n	RA	FA
	1820	809(44.5)	1011(55.5)
Austria, n(%)	50	8 (16.0)	42 (84.0)
Belgium, n(%)	7	0 (0.0)	7 (100.0)
Brazil, n(%)	75	22 (29.3)	53 (70.7)
Canada, n(%)	88	47 (53.4)	41 (46.6)
France, n(%)	717	544 (75.9)	173 (24.1)
Germany, n(%)	54	13 (24.1)	41 (75.9)
Greece, n(%)	72	3 (4.2)	69 (95.8)
Italy, n(%)	25	18 (72.0)	7 (28.0)
Norway, n(%)	53	45 (84.9)	8 (15.1)
Peru, n(%)	2	0 (0.0)	2 (100.0)
Poland, n(%)	27	18 (66.7)	9 (33.3)
Russia, n(%)	306	11 (3.6)	295 (96.4)
Serbia, n(%)	128	6 (4.7)	122 (95.3)
Spain, n(%)	159	34 (21.4)	125 (78.6)
United Kingdom, n(%)	57	40 (70.2)	17 (29.8)

Table S2. Logistic regression model (propensity score model) of access site and baseline characteristics.

Variables	Degree of freedom	Wald	p-values
Age, year	1	0.05	0.830
Female	1	0.02	0.884
Weight, kg	1	4.44	0.035
History of hypertension	1	1.93	0.164
History of diabetes	1	0.11	0.742
Heart rate, bpm	1	4.50	0.034
Systolic blood pressure, mmHg	1	3.54	0.060
Killip class > I	1	4.04	0.044
Inferior MI	1	0.74	0.390
Sum ST elevation at baseline, mm	1	0.10	0.753
Q waves at baseline	1	0.50	0.479
Time from symptom onset to randomization, hour	1	4.97	0.026
Country of enrolment	14	460.17	<0.001

Countries and Investigators

In addition to the authors, the following investigators participated in the STREAM study:

Austria (52 patients): A Kaff, R Malzer, D Sebald, D Glogar, M Gyöngyösi, F Weidinger, H Weber, G Gaul, F Chmelizek, S Seidl, M Pichler, I Pretsch.
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Brazil (79 patients): JFK Saraiva, ALF Sparenberg, JA Souza, JBM Moraes, FM Sant'anna, E Tarkieltaub, JR Hansen, EM Oliveira, O Leonhard.
Canada (92 patients): W Cantor, M Senaratne.
France (751 patients): E Aptecar, P Asseman, L Belle, O Belliard, J Berland, A Berthier, C Besnard, A Bonneau, E Bonnefoy, M Brami, G Canu, G Capellier, S Cattan, D Champagnac, P Chapon, B Cheval, J Claudel, P Cohen Tenoudji, P Coste, V Debierre, R Domergue, K Echahed, C El Khoury, E Ferrari, P Garrot, P Henry, B Jardel, R Jilwan, V Julie, R Ketelers, F Lapostolle, J Le Tarnec, B Livarek, Y Mann, X Marchand, F Pajot, T Perret, P Petit, V Probst, A Ricard Hibon, C Robin, A Salama, E Salengro, D Savary, F Schiele, L Soulat, X Tabone, P Taboulet, M Thicoïpe, J Torres, C Tron, G Vanzetto, L Villain-Coquet.
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Poland (29 patients): A Glowka, P Kulus.
Russian Federation (327 patients): S Kalinina, A Bushuev, O Barbarash, N Tarasov, I Fomin, E Makarov, V Markov, A Danilenko, E Volkova, A Frolenkov, N Burova, A

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Spain (167 patients): A Ruiz, A García-Alcántara, M Martínez, J Díaz, MA, Paz, FL Manzano, C Martín, C Macaya, E Corral, JJ Fernández, F Martín, R, García.
United Kingdom (60 patients): N Siriwardena, O Rawstorne, A Baumbach, G Manoharan, I Menown, S McHechan, D Morgan.