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 post fibrinolytic 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.

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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). RA in patients treated with a fibrinolytic pharmacoinvasive strategy (PI) has had limited exploration, 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. 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, 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. 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.

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. 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. Briefly, a stroke review independent panel adjudicated all strokes centrally. The Global Use of Strategies to Open Occluded Arteries (GUSTO) definition of bleeding 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. 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
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.

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

|                  | All          | PI RA  | P Value | PI FA  | P Value | pPCI RA | P Value | pPCI 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 ≥1, 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 |
| O 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.

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

|                      | All                     | RA           | FA           | P Value | PI                     | RA           | FA           | P Value | RA           | FA           | P Value |
|----------------------|-------------------------|--------------|--------------|---------|-------------------------|--------------|--------------|---------|--------------|--------------|---------|
| 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 | —                       | —            | —            | —       | —                       | —            | —            | —       | —            | —            | —       |
| Symptom onset to     |                         |              |              |         |                         |              |              |         |              |              |         |
| sheath insertion, min| 624 (260, 1320)         | 616 (268, 1218) | <0.001       | 242 (58.0) | 115 (24.1) | <0.001 | 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           |              |              |         |              |              |              |         |              |              |         |
| 0/1                  | 16 (2.4)               | 27 (3.1)     | 11 (3.3)     | 9 (2.4)   | 5 (1.5)    | 22 (3.7) | 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                 |              |              |         |              |              |         |
| <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.
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
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). 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. 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) and Radial versus femoral access for coronary intervention (RIVAL; 12%) 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, a higher proportion of major overall and

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**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.
major access-site bleeding was noted in the current study; for instance, radial versus femoral, respectively, in RIVAL 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). 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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Disclosures
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References
1. Karrwoni W, Vyas A, Giacomino B, Schweizer M, Blevins A, Girotra S, Horwitz P. Radial versus femoral access for primary percutaneous interventions in ST-segment elevation myocardial infarction patients: a meta-analysis of randomized controlled trials. JACC Cardiovasc Interv. 2013;8:14–23.
2. Romagnoli E, Biondi-Zoccai G, Sciahbasi A, Politi L, Rigattieri S, Pendenza G, Summoria F, Patrizi R, Borghi A, Di Russo C, Moretti C, Agostoni P, Loschiavo P, Lioy E, Sheiban I, Sangiorgi G. Radial versus femoral randomized investigation in ST-segment elevation acute coronary syndrome: the RIFLE-STEACS (Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome) study. J Am Coll Cardiol. 2012;60:2481–2489.
3. Bernat I, Horak D, Stasek J, Mates M, Pesek J, Ostadal P, Hrabos V, Dusek J, Kozaj J, Sembera Z, Bittko M, Aschermann O, Smid M, Polansky P, Mawiri AA, Vojaecik J, Bis J, Costerousse O, Bertrand O, Rokyta R. ST-segment elevation myocardial infarction treated by radial or femoral approach in a multicenter randomized clinical trial: the STEMI-RADIAL trial. J Am Coll Cardiol. 2014;63:964–972.
4. Rabj K, Mamais M, Anderson S, Bhata G, Routledge H, Belder MD, Ludman P, Fraser D, Nolan J. Access site practice and procedural outcomes in relation to clinical presentation in 439,947 patients undergoing percutaneous coronary intervention in the United Kingdom. JACC Cardiovasc Interv. 2015;8:20–29.
5. Hamon M, Coste P, Van’t Hof A, Ten Berg J, Clemenmons P, Tabone X, Benamer H, Kristensen SD, Cavallini C, Marzocchi A, Hamm C, Canic V, Bernstein D, Anthopoulos P, Deliargyris EN, Steg PG. Impact of arterial access site on outcomes after primary percutaneous coronary intervention: prespecified subgroup analysis from the EUROMAX trial. Circ Cardiovasc Interv. 2015;8:e002049.

6. Jolly SS, Amlani S, Hamon M, Yusuf S, Mehta SR. Radial versus femoral access for coronary angiography or intervention and the impact on major bleeding and ischemic events: a systematic review and meta-analysis of randomized trials. Am Heart J. 2009;157:132–140.

7. Mehta SR, Jolly SS, Cairns J, Niemela K, Rao SV, Cheema AN, Steg PG, Cantor WJ, Dzavik V, Budaj A, Rokoss M, Valentin V, Gao P, Yusuf S; Investigators R. Effects of radial versus femoral artery access in patients with acute coronary syndromes with or without ST-segment elevation. J Am Coll Cardiol. 2012;60:2490–2499.

8. Valgimigli M, Gagnor A, Calabro P, Frigoli E, Leonardi S, Zaro T, Rubartelli P, Briguori C, Ando G, Repetto A, Limbruno U, Cortese B, Sgangerla P, Lapi A, Galli M, Colangelo S, Ierna S, Ausiello A, Presbitero P, Sardella G, Varbella F, Esposito G, Santarelli A, Tresoldi S, Nazzaro M, Zingarelli A, de Cesare N, Rigattieri S, Tosi P, Palmieri C, Brugaletta S, Rao SV, Heg D, Rothenbuhler M, Vranckx P, Juni P; Investigators M. Radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: a randomised multicentre trial. Lancet. 2015;385:2465–2476.

9. Hamon M, Pristipino C, Di Micio V, Nolan J, Ludwig J, Tabaro M, Sabate M, Mauri-Ferre J, Huber K, Niemela K, Haude M, Wijns W, Dudek D, Fajadet J, Kiemenie JF; European Association of Percutaneous Cardiovascular I, Working Group on Acute Cardiac Care of the European Society of C, Working Group on Thrombosis on the European Society of C. Consensus document on the radial approach in percutaneous cardiovascular interventions: position paper by the European Association of Percutaneous Cardiovascular Interventions and Working Groups on Acute Cardiac Care** and Thrombosis of the European Society of Cardiology. EuroIntervention. 2013;8:1242–1251.

10. Rao SV, Tremmel JA, Gilchrist IC, Shah PB, Gulati R, Shroff AR, Crisco V, Woody W, Zoghbi G, Duffy PL, Sanghvi K, Krucoff MW, Skelding KA, Patel T, Pancholy SB; Society for Cardiovascular A, Intervention after STEMI undergoing early PCI following intravenous thrombolysis. J Invasive Cardiol. 2012;24:412–416.

11. Jollamy C, Pelle JP, McKay DF, Behan M, Slack R, Oldroyd K, Berry C. Clinical outcomes following radial versus femoral artery access in primary or rescue percutaneous coronary intervention in Scotland: retrospective cohort study of 4534 patients. Heart. 2012;98:552–557.

12. Welsh RC, Van de Werf F, Westerhout CM, Goldstein P, Gershlick AH, Wilcox RG, Danays T, Bluhmki E, Lopes RD, Steg PG, Armstrong PW. Outcomes of a pharmacoinvasive strategy for successful versus failed fibriolysis and primary percutaneous intervention in acute myocardial infarction from the STRategic Reperfusion Early After Myocardial Infarction [STREAM] study. Am J Cardiol. 2014;114:811–819.

13. Armstrong P, Gershlick A, Goldstein P, Wilcox R, Danays T, Lambert Y, Sulimov V, Ortiz FR, Ostojc M, Welsh R, Carvalho A, Nanas J, Amtz H, Halvorsen S, Huber K, Grajek S, Fresco C, Bluhmki E, Regelin A, Vandenberge K, Bogaerts K, Van de Werf F; STREAM Investigative Team. Fibriolysis or primary PCI in ST-segment elevation myocardial infarction. N Engl J Med. 2013;368:1379–1387.

14. Armstrong P, Gershlick A, Goldstein P, Wilcox R, Danays T; STREAM Steering Committee. The strategic reperfusion early after myocardial infarction (STREAM) study. Am Heart J. 2010;160:30–35.

15. Buller CE, Fu Y, Mahaffey KW, Todaro TG, Adams P, Westerhout CM, White HD, van’t Hof AW, Van de Werf FJ, Wagner GS, Granger CB, Armstrong PW. ST-segment recovery and outcome after primary percutaneous coronary intervention for ST-elevation myocardial infarction: insights from the Assessment of Pexelizumab in Acute Myocardial Infarction (APEX-AMI) trial. Circulation. 2008;118:1335–1346.

16. Patel T, McGinn T, Garcia E, Kodali S, Harrington P, Murphy SA, Newby DE; TIMI 18 Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. The GUSTO investigators. N Engl J Med. 1993;329:673–682.

17. Kerth T, Walker A, Glynn R, Chan K, Gaziano J, Berger K, Robins J. Results of multivariable logistic regression, propensity matching, propensity adjustment, and propensity-based weighting under conditions of nonuniform effect. Am J Epidemiol. 2005;163:262–270.

18. Bertrand O, Patel T. Radial approach for primary percutaneous coronary intervention: ready for prime time? J Am Coll Cardiol. 2012;60:2500–2503.

19. Radial vascular access in patients undergoing rescue percutaneous coronary intervention after fibrinolytic therapy. JACC Cardiovasc Interv. 2015;8:1868–1876.
Table S1. Radial vs. Femoral access according to country of enrollment.

| Country          | n   | RA   | FA   |
|------------------|-----|------|------|
| 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:

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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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