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Access Site Crossover in Patients with Acute Coronary Syndrome Undergoing Invasive Management

Felice Gragnano, MD,[a,b] Mattia Branca,[c] Enrico Frigoli, MD,[c] Sergio Leonardi, MD, MHS,[d] Pascal Vranckx, MD, PhD,[e,f] Dario Di Maio, MD,[b] Emanuele Monda, MD,[b] Luigi Fimiani, MD,[g] Vincenzo Fioretti, MD,[h] Salvatore Chianese, MD,[h] Fabrizio Esposito, MD,[h] Michele Franzese, MD,[h] Martina Scalise, MD,[h] Claudio D'Angelo, MD,[g] Renato Scalise, MD,[g] Gabriele De Blasi, MD,[g] Giuseppe Andò, MD, PhD,[g] Giovanni Esposito, MD, PhD,[h] Paolo Calabrò, MD, PhD,[b] Stephan Windecker, MD,[a] Giovanni Pedrazzini, MD,[i] Marco Valgimigli, MD, PhD[a,i]

On behalf of the MATRIX trial Investigators

From the [a]Department of Cardiology, Inselspital, University of Bern; [b]Division of Cardiology, Department of Translational Medicine, University of Campania "Luigi Vanvitelli", Caserta, Italy; [c]Clinical Trials Unit, University of Bern, Bern, Switzerland; [d]University of Pavia and Fondazione IRCCS Policlinico S.Matteo, Pavia, Italy; [e]Department of Cardiology and Critical Care Medicine, Hartcentrum Hasselt, Jessa Ziekenhuis, Belgium; [f]Faculty of Medicine and Life Sciences, University of Hasselt, Hasselt, Belgium; [g]Unit of Cardiology, Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy; [h]Department of Advanced Biomedical Sciences, Federico II University of Naples, Naples, Italy; [i]Cardiocentro Ticino, Lugano, Switzerland.

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Address for Correspondence:
Prof. Marco Valgimigli
Cardiocentro Ticino
CH- 6900 Lugano, Switzerland
marco.valgimigli@cardiocentro.org
Phone/Fax: +41 91 805 33 47
Twitter handle: @vlgmrc

ABSTRACT

Objectives. To assess the impact of access site crossover in patients with acute coronary syndrome (ACS) undergoing invasive management via radial or femoral access.
Background. There is limited data on the clinical implications of access site crossover.
Methods. In the MATRIX-Access trial, 8,404 ACS patients were randomized to radial or femoral access. Patients undergoing access site crossover or successful access site were investigated. Thirty-day co-primary outcomes were a composite of death, myocardial infarction, or stroke (major adverse cardiovascular events, MACE), and a composite of MACE or BARC type 3 or 5 bleeding (net adverse cardiovascular events, NACE).
Results. Access site crossover occurred in 183 (4.4%) of 4,197 patients in the radial group (mainly to femoral access) and 108 (2.6%) of 4,207 patients in the femoral group (mainly to radial access). At multivariate analysis, the risk of co-primary outcomes was not significantly higher with radial crossover compared with successful radial (MACE, adjusted risk ratio [adjRR]:1.25; CI:0.81-1.93; p=0.32; NACE, adjRR:1.40; CI:0.94-2.06; p=0.094) or successful femoral access (MACE, adjRR:1.17; CI:0.76-1.81; p=0.47; NACE, adjRR:1.26; CI:0.86-1.86; p=0.24). Access site-related BARC 3 or 5 bleeding was higher with radial crossover than successful radial access. Femoral crossover remained associated with higher risks of MACE (adjRR:1.84; CI:1.18-2.87; p=0.007) and NACE (adj RR:1.69; CI:1.09-2.62; p=0.019) compared with successful femoral access. Results remained consistent after excluding patients with randomized access not attempted.
Conclusions. Crossover from radial to femoral access abolishes the bleeding benefit offered by the radial over femoral artery but does not appear to increase the risk of MACE or NACE compared with successful radial or femoral access.

Trial registration ClinicalTrials.gov number NCT01433627.

Keywords: Radial access; Femoral access; Crossover; Percutaneous coronary intervention; Acute coronary syndrome.

Condensed Abstract
Using data from the MATRIX trial, we investigated the incidence, characteristics, and prognostic implications of access site crossover in patients with acute coronary syndrome invasively managed via randomly allocated radial (n=4,197) or femoral (n=4,207) access. After adjustment, the risk of MACE and NACE was not significantly higher in patients with radial crossover (n=183) compared with successful radial or femoral access, whereas there was an increased risk of access site-related BARC 3 or 5 bleeding with radial crossover compared with successful radial access. Femoral crossover (n=108) remained associated with higher risks of MACE and NACE compared with successful femoral access.

Abbreviations List

ACS, acute coronary syndrome
AdjRR, adjusted rate ratio
BARC, Bleeding Academic Research Consortium
CI, confidence intervals
GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator
MACE, major adverse cardiovascular events
MATRIX, Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX
NACE, net adverse clinical events
PCI, percutaneous coronary intervention
RR, rate ratio
STEMI, ST-segment-elevation myocardial infarction
TIMI, Thrombolysis in Myocardial Infarction

INTRODUCTION

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

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

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

METHODS

Study design and participants

This is a pre-specified sub-analysis of the MATRIX-Access, a randomized, multicenter, superiority trial comparing radial versus femoral access in patients with ACS, with or without ST-segment elevation, undergoing invasive management (ClinicalTrials.gov; NCT01433627). The rationale, design, and main results of the MATRIX program have been previously reported (4,5,16). In brief,

patients were randomized (1:1) to radial or femoral access for diagnostic angiography and percutaneous coronary intervention (PCI) if indicated. Patients were eligible if they presented with ACS with or without ST-segment elevation, were about to receive invasive management, and the interventional cardiologist was willing to proceed with either the radial or femoral access with expertise for both, including at least 75 coronary interventions performed and at least 50% of interventions in ACS via the radial artery during the previous year (4,16). Access site management during and after the procedure was left to the discretion of the treating physician (16,17). The use of anticoagulants outside the MATRIX protocol was not allowed. Bivalirudin was administered according to the approved product labeling. Unfractionated heparin was dosed at 70-100 U/kg in patients not receiving glycoprotein IIb/IIIa inhibitors and 50-70 U/kg in patients receiving glycoprotein IIb/IIIa inhibitors. The use of all other medications was allowed as per guidelines.

Access site crossover definition

All participants in the MATRIX-Access trial were considered eligible for the present analysis. Based on the arterial access used to perform coronary catheterization at index procedure, patients were categorized into four groups: (a) radial crossover, if the operator failed to start or complete the procedure via the randomly assigned radial access and required to crossover to the femoral or brachial access; (b) femoral crossover, if the operator failed to start or complete the procedure via the randomly assigned femoral access and required to crossover to the radial or brachial access; (c) successful radial or (d) successful femoral access, if the operator successfully performed the procedure via the randomly assigned access. Patients undergoing crossover from radial to ulnar artery, from radial to contralateral radial artery, or from femoral to contralateral femoral artery (internal crossover), were not considered as crossover patients. Clinical and/or procedural reasons determining radial or femoral crossover were collected and categorized as follows: (1) access site not attempted, if the randomly allocated access was not chosen by the operator as initial access for

any clinical reason; (2) issues in arterial puncture or sheath insertion; (3) failure to complete coronary angiography; and (4) failure to complete PCI.

Follow-up and study outcomes

In the MATRIX program, the two co-primary outcomes at 30 days were major adverse cardiovascular events (MACE), defined as the composite of all-cause death, myocardial infarction, or stroke, and net adverse clinical events (NACE), defined as the composite of MACE or major bleeding not related to coronary artery bypass grafting (Bleeding Academic Research Consortium [BARC] type 3 or 5) (16). Secondary outcomes included each component of the co-primary outcomes, cardiovascular death, access site-related and non-access site-related bleeding events, and definite or probable stent thrombosis. Bleeding was defined according to the BARC (Bleeding Academic Research Consortium), TIMI (Thrombolysis In Myocardial Infarction), and GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator) scales. An independent clinical events committee, blinded to treatment allocation, adjudicated all adverse events.

Statistical analysis

The MATRIX-Access trial was powered for superiority on the two co-primary outcomes at 30 days, expecting a rate reduction of 30% that corresponded to a rate ratio (RR) of 0.70. All analyses were performed following the intention-to-treat principles, and clinical events at 30 days after randomization were considered. Primary and secondary outcomes were analyzed as time-to-first event using the Mantel-Cox method, accompanied by log-rank tests to calculate corresponding two-sided p-values. For the present analysis, to take into account differences in baseline characteristics among study groups, dedicated multivariate models were implemented to obtain adjusted outcomes, including as variables: (a) age, sex, diabetes, smoking, previous myocardial infarction, previous coronary artery bypass grafting, previous transient ischemic attack or stroke, type of ACS, ejection fraction, estimated glomerular filtration rate, Killip class, glycoprotein IIb/IIIa inhibitors, intra-

aortic balloon pump, staged procedure, left main PCI, sheath size, post-procedural TIMI flow 3, and total contrast volume for the comparison between radial crossover and successful radial access; (b) age, diabetes, smoking, previous myocardial infarction, previous coronary artery bypass grafting, type of ACS, ejection fraction, estimated glomerular filtration rate, Killip class, glycoprotein IIb/IIIa inhibitors, intra-aortic balloon pump, staged procedure, left main PCI, sheath size, post-procedural TIMI flow 3, and total contrast volume for the comparison between radial crossover and successful femoral access, and (c) body-mass-index, diabetes, previous PCI, peripheral vascular disease, type of ACS, lytic therapy, ticagrelor before cath-lab, unfractionated heparin before cath-lab, post-PCI bivalirudin regimen, sheath size, and total contrast volume for the comparison between femoral crossover and successful femoral access. Sensitivity analyses were conducted in patients undergoing access site crossover after an unsuccessful attempt via the randomly allocated access (i.e., excluding patients without an initial attempt from the assigned access). Sub-groups analysis according to the clinical presentation was performed to estimate possible interaction terms across comparisons. All analyses were performed using the statistical software Stata 15.1.

RESULTS

Study population

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

Clinical and procedural characteristics

Baseline and procedural characteristics of the study population are detailed in **Table 1 and Online Table 1.** Compared with patients undergoing successful radial access, patients with radial crossover were approximately 5 years older and more frequently females; had more often a history of

myocardial infarction, coronary artery bypass grafting, and renal failure; presented more often with STEMI or advanced Killip class, and underwent more frequently left main coronary intervention, hemodynamic support, and unsuccessful PCI. Compared with patients receiving successful femoral access, patients with femoral crossover had a higher body-mass-index, more often a history of diabetes and peripheral vascular disease, and less frequently a diagnosis of STEMI on admission. Both crossover groups had a higher prevalence of diabetes and were exposed to higher contrast volume, longer fluoroscopy and procedural times than patients undergoing successful access site. Compared with the femoral crossover group, patients with radial crossover were older, had lower body-mass-index and estimated glomerular filtration rate, presented more frequently with STEMI, and showed less often TIMI 3 flow in all treated lesions after the intervention.

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

Clinical outcomes

Unadjusted outcomes at 30 days

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

Multivariate adjusted outcomes at 30 days

Radial crossover vs. successful radial access

After multivariate adjustment, the risks of MACE (adjusted RR [adjRR]:1.25; 95% confidence interval [CI]:0.81-1.93; p=0.32), NACE (adjRR:1.40; 95% CI:0.94-2.06; p=0.090), and their individual components did not differ between patients undergoing radial crossover or successful radial access. Yet, radial crossover remained associated with a significantly higher risk of bleeding

– including access site-related BARC 3 or 5 (adjRR:9.65; 95% CI:2.49-37.41; p=0.001), overall BARC 2, 3 or 5 (adjRR:1.80; 95% CI:1.02-3.16; p=0.041), and access site-related BARC 2, 3 or 5 events (adjRR:6.65; 95% CI:3.60-12.26; p<0.001) – and surgical access site repair or transfusions (adjRR:2.60; 95% CI:1.01-6-67; p=0.047) **(Central Illustration, Table 2, and Online Table 2)**.

Radial crossover vs. successful femoral access

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

Femoral crossover vs. successful femoral access

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

Sensitivity analysis

Sensitivity analyses showed consistent results in patients undergoing radial (n=154) or femoral (n=53) crossover after an unsuccessful attempt. After excluding patients with assigned access site not attempted, both crossover groups confirmed a higher crude rate of events than the successful access groups **(Table 4 and Online Table 4).** Compared with those undergoing successful radial access, patients with radial crossover showed a higher adjusted risk of NACE and bleeding events –

mainly related to the access site. The radial crossover group also showed an increased risk of access site-related BARC 2, 3 or 5 bleeding compared with the successful femoral access group, but no difference in terms of ischemic or fatal endpoints. Patients with femoral crossover had a significant and borderline increase in the risk of MACE, NACE, all-cause mortality, and BARC 2, 3 or 5 bleeding (p-values of 0.049, 0.062, 0.057, and 0.016, respectively) compared with those undergoing successful femoral access.

Sub-groups analyses

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

DISCUSSION

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

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

2) Crossover from femoral to mainly radial access occurred more frequently in patients with higher body-mass-index, established diabetes and/or peripheral artery disease, and non-ST-elevation ACS on admission. Femoral crossover was not associated with a higher risk of major bleeding. However, despite extensive multivariable adjustment, the risk of both co-primary endpoints, death, stroke, and stent thrombosis was higher with femoral crossover compared with successful femoral access. Sub-group analyses suggested that this risk was particularly pronounced among STEMI patients.

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

Incidence and characteristics of access site crossover

In contemporary PCI cohorts, radial crossover has been reported in up to 10% of cases, though this rate varies widely according to patient's characteristics, procedural aspects, and operators' expertise (10–15,18,19). In the RIVAL trial (3), enrolling 7,021 ACS patients with and without ST-segment elevation, the incidence of crossover was 7.6% in patients randomized to radial access, and 2.0% in those randomized to femoral access, while in the RIFLE-STEACS trial (6), including 1,001 STEMI patients, the corresponding figures were 9.4% and 2.8%. In large observational studies, including patients undergoing elective or urgent coronary catheterization, access site crossover has been reported in 4% to 8% of cases for radial access, and in about 2% of cases for femoral access (10–

15). In the MATRIX trial, access site crossover occurred in 4.4% of patients randomized to radial access and 2.6% of those randomized to femoral access, and this rate did further decrease to 3.7% and 1.3%, respectively, after excluding patients in whom the randomly allocated access was not attempted by the operator. The relatively low rate of radial crossover in the MATRIX trial should be interpreted in the context of the high radial proficiency of each participating operator. Similar to previous reports, the principal reasons for crossover in our cohort were issues related to the arterial puncture or sheath insertion, vessel tortuosity, vasospasm, and the operator's decision not to attempt the randomized access (10–12).

Impact of radial access crossover on procedural and clinical outcomes

A few studies have investigated procedural and clinical outcomes in patients with radial crossover compared with successful radial or femoral access (10–13,15). Among 241 patients with STEMI undergoing primary PCI (15), radial crossover was associated with a slight but significant increase in time to gain vascular access and procedure duration compared with successful radial access (of approximately 6 and 14 minutes, respectively) or successful femoral access (of approximately 5 and 8 minutes, respectively). These results are in line with our findings as we observed a significant, although modest, increase in total procedure time, fluoroscopy time, and contrast volume – of approximately 15 minutes, 5 minutes, and 25 ml, respectively – in the two crossover groups compared with the successful access groups.

With respect to clinical outcomes, Abdelaal et al. (10) recently reported the prognostic impact of radial access crossover in 2,020 STEMI patients treated with primary PCI from a single high-volume radial center. Patients requiring radial crossover (7.7% of the study population) had a higher rate of major bleeding and vascular complications, as well as 30-day mortality compared with those undergoing PCI via successful radial access. At multivariate analysis, conversion to femoral access after radial failure remained associated with a 2-fold increase in the risk of mortality (10). More data from the same center (11) as well as other institutions (15) have consistently shown that radial

crossover is associated with a higher incidence of ischemic and/or bleeding events compared with successful radial access. However, these studies were potentially limited by the single-center design, the small sample size, the non-random allocation of the access site, and the absence of adjudicated events (10,11,15). In the present analysis, including 8,404 ACS patients from 78 centers with randomly assigned access and adjudicated endpoints, ischemic and bleeding events at 30 days were seemingly worse in both crossover groups compared with patients who received successful intervention via the randomly assigned access site, either the radial or femoral artery. However, the risk profile of both crossover groups was significantly worse compared with the successful access site groups. After extensive adjustment for all measured confounders, radial crossover was no longer associated with higher ischemic risk compared with successful radial or femoral access. Yet, radial crossover remained associated with a higher risk of access site-related major and minor bleeding occurrences compared with successful radial access to the extent that this subset of patients incurred at least the same risk of access site-related major bleeding compared with patients successfully treated via the femoral access. These results remained consistent after excluding patients in whom the operator elected not to attempt the randomized access for clinical reasons. Our findings can be easily explained by the need to puncture a second femoral or brachial access site, and both alternatives have been associated with a higher risk of bleeding compared with the radial artery (3–5,19). Altogether, our results are reassuring and support the concept of the radial first strategy, considering that failure to complete the intervention via the radial artery requiring crossover to femoral access does not expose patients to heightened risks of ischemic outcomes, while understandably dissipate the bleeding benefit observed with radial access. In this context, the upfront identification of patients at high risk for radial crossover could allow operators to anticipate technical difficulties and select optimal access site in each individual patient. However, no standardized and validated tool exists to predict the risk of radial crossover and/or select specific patient cohorts that could be better treated via primary femoral access. Hence, future research addressing this issue remains desirable.

Prognostic implications of femoral access crossover

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

Study limitations

Although the present analysis is the largest evaluating patients undergoing radial or femoral access with and without crossover, the MATRIX-Access was not powered to explore differences in outcomes across these subgroups. As such, the current analysis might be subject to a type II error. In a non-negligible proportion of patients, especially in the femoral group, access site crossover

followed the operator's decision not to proceed via the randomly assigned access. Of note, study results remained largely consistent after excluding these cases, suggesting that our conclusions are valid and can be similarly applied to crossover patients with or without attempted access site. Access site management was left to the discretion of the operator. Thus, all procedures related to patient preparation, puncture technique, medications (i.e., spasmolytic cocktail), and materials were used as per local practice. This introduces a certain variability but reflects current practice in which these procedures remain not standardized. Our data and conclusions apply to the context of the MATRIX trial in which all participating centers were experienced with both radial and femoral access; therefore, similar results may not apply in centers at low radial or femoral expertise.

CONCLUSIONS

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

PERSPECTIVES

WHAT IS KNOWN?

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

WHAT IS NEW?

Access site crossover from radial to the femoral access abolishes the bleeding benefit offered by the radial over femoral artery but does not seem to increase the risk of MACEs or NACEs as compared with primary successful radial or femoral access. Femoral access crossover remains associated with an increased adjusted risk of fatal events and non-fatal ischemic outcomes, particularly among STEMIs.

WHAT IS NEXT?

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

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Figure Legends

Figure 1. Crossover data for radial and femoral groups. (A) Reasons for radial access crossover. (B) Reasons for femoral access crossover. (C) Access site issues causing crossover after successful sheath insertion in patients undergoing radial or femoral crossover. PCI = percutaneous coronary intervention.

Central Illustration. Summary of ischemic and bleeding endpoints in patients with access site crossover or successful access via radial or femoral artery. (A) In the MATRIX trial, radial crossover (mainly to femoral access) and femoral crossover (mainly to radial access) occurred in 4.4% and 2.6% of cases, respectively. (B) Radial crossover was associated with a higher risk of BARC 3 or 5 access site bleeding compared with successful radial access. Radial crossover abolished the bleeding benefit of radial access over femoral access but did not expose patients to higher risks of MACEs or NACEs as compared with successful femoral access. Femoral crossover was associated with a higher risk of MACE and NACE than successful femoral access.
BARC = Bleeding Academic Research Consortium; MACE = major adverse cardiovascular events; NACE = net adverse clinical events.

Table 1. Baseline characteristics of radial and femoral groups

Baseline characteristics	Radial crossover (n=183)	Successful radial (n=4,014)	Femoral crossover (n=108)	Successful femoral (n=4,099)	p-value[y]	p-value[z]	p-value[x]
Age, years	69.8 (11.3)*	65.4 (11.8)	65.5 (12.8)	65.9 (11.8)	<0.001	<0.001	0.68
≥75 years	69 (37.7%)	1,004 (25.0%)	30 (27.8%)	1,079 (26.3%)	<0.001	<0.001	0.73
Male sex	123 (67.2%)	3,003 (74.8%)	77 (71.3%)	2,969 (72.4%)	0.021	0.12	0.79
Body-mass-index, kg/m²	27.0 (4.1)*	27.1 (4.2)	28.2 (5.7)	27.0 (4.1)	0.87	0.97	0.003
Diabetes mellitus	53 (29.0%)	906 (22.6%)	37 (34.3%)	907 (22.1%)	0.044	0.030	0.002
Insulin-dependent	12 (6.6%)*	197 (4.9%)	15 (13.9%)	242 (5.9%)	0.31	0.71	<0.001
Current smoker	41 (22.4%)	1,418 (35.3%)	32 (29.6%)	1,396 (34.1%)	<0.001	0.001	0.33
Hypercholesterolemia	83 (45.4%)	1,716 (42.8%)	51 (47.2%)	1,841 (44.9%)	0.48	0.90	0.63
Hypertension	127 (69.4%)	2,498 (62.2%)	74 (68.5%)	2,612 (63.7%)	0.050	0.11	0.30
Previous myocardial infarction	39 (21.3%)	546 (13.6%)	22 (20.4%)	596 (14.5%)	0.003	0.011	0.091
Previous PCI	34 (18.6%)	576 (14.3%)	23 (21.3%)	562 (13.7%)	0.11	0.062	0.024
Previous CABG	11 (6.0%)	100 (2.5%)	4 (3.7%)	142 (3.5%)	0.003	0.069	0.89
Previous TIA or stroke	15 (8.2%)	180 (4.5%)	6 (5.6%)	224 (5.5%)	0.019	0.11	0.96
Peripheral vascular disease	17 (9.3%)*	324 (8.1%)	22 (20.4%)	350 (8.5%)	0.55	0.72	<0.001
Renal failure	8 (4.4%)	38 (0.9%)	3 (2.8%)	56 (1.4%)	<0.001	0.001	0.21
Dialysis	2 (1.1%)	2 (0.1%)	0 (0.0%)	4 (0.1%)	0.010	0.024	>0.99
Clinical presentation							
STEMI	101 (55.2%)*	1,900 (47.3%)	41 (38.0%)	1,968 (48.0%)	0.037	0.057	0.039
NSTE-ACS	82 (44.8%)*	2,114 (52.7%)	67 (62.0%)	2,131 (52.0%)			
NSTE-ACS, troponin positive	73 (39.9%)*	1,881 (46.9%)	64 (59.3%)	1,868 (45.6%)	0.064	0.13	0.004
Heart rate, bpm	75.7 (15.9)	76.3 (16.6)	79.1 (18.7)	75.9 (16.8)	0.59	0.84	0.050
Systolic arterial pressure, mmHg	135.4 (27.3)	138.6 (25.4)	139.0 (30.4)	138.8 (25.5)	0.095	0.078	0.94
Left ventricular ejection fraction, %	48.9 (11.0)	51.4 (9.5)	51.2 (9.8)	50.8 (9.8)	0.001	0.012	0.74
eGFR, ml/ min/1.73 m²	76.0 (27.4)*	84.5 (25.3)	84.7 (32.9)	83.3 (25.3)	<0.001	<0.001	0.57
eGFR <60 ml/min/1.73 m²	49 (27.2%)	651 (16.3%)	24 (22.4%)	691 (17.0%)	<0.001	<0.001	0.13

Cardiac arrest at presentation	5 (2.7%)	80 (2.0%)	2 (2.0%)	81 (2.0%)	0.53	0.44	0.89
Killip class					<0.001	<0.001	0.27
I	151 (82.5%)	3,645 (90.8%)	92 (85.2%)	3,708 (90.5%)			
II	20 (10.9%)	248 (6.2%)	11 (10.2%)	290 (7.1%)			
III	2 (1.1%)	86 (2.1%)	4 (3.7%)	75 (1.8%)			
IV	10 (5.5%)	35 (0.9%)	1 (0.9%)	26 (0.6%)			
Medications before catheterization							
Lytic therapy	5 (2.7%)	89 (2.2%)	0 (0.0%)	104 (2.5%)	0.64	0.86	0.093
Aspirin	171 (93.4%)	3,785 (94.3%)	106 (98.1%)	3,848 (93.9%)	0.62	0.81	0.065
Clopidogrel	94 (51.4%)	1,921 (47.9%)	58 (53.7%)	1,939 (47.3%)	0.35	0.28	0.18
Prasugrel	18 (9.8%)	467 (11.6%)	10 (9.3%)	458 (11.2%)	0.45	0.57	0.53
Ticagrelor	42 (23.0%)	936 (23.3%)	19 (17.6%)	1,010 (24.6%)	0.90	0.60	0.092
Enoxaparin	22 (12.0%)*	665 (16.6%)	26 (24.1%)	716 (17.5%)	0.10	0.056	0.075
Fondaparinux	15 (8.2%)*	413 (10.3%)	17 (15.7%)	451 (11.0%)	0.36	0.23	0.12
ACE inhibitors	54 (29.5%)	1,199 (29.9%)	37 (34.3%)	1,264 (30.8%)	0.91	0.70	0.44
Angiotensin II receptor blocker	19 (10.4%)	431 (10.7%)	16 (14.8%)	446 (10.9%)	0.87	0.83	0.19
Statins	75 (41.0%)	1,737 (43.3%)	49 (45.4%)	1,814 (44.3%)	0.54	0.38	0.81
Beta-blockers	72 (39.3%)	1,622 (40.4%)	45 (41.7%)	1,730 (42.2%)	0.77	0.44	0.91
Warfarin	3 (1.6%)	69 (1.7%)	3 (2.8%)	61 (1.5%)	0.93	0.86	0.27
Proton pump inhibitor	92 (50.3%)	2,066 (51.5%)	59 (54.6%)	2,133 (52.0%)	0.75	0.64	0.59
Unfractionated heparin	54 (29.5%)	1,185 (29.5%)	22 (20.4%)	1,215 (29.6%)	0.99	0.96	0.036
Bivalirudin	0 (0%)	4 (0.1%)	0 (0.0%)	2 (0.1%)	>0.99	>0.99	>0.99
Glycoprotein IIb/IIIa inhibitors	0 (0%)	8 (0.2%)	0 (0.0%)	6 (0.1%)	>0.99	>0.99	>0.99

Depicted are sample sizes (n) and counts (%); means (±standard deviations) or medians (25%-75% interquartile range).
P-values were generated with Chi-Square or Fisher Exact test if categorical variable, t-test or Wilcoxon test if continuous variable.
*$p<0.05$ for radial crossover group versus femoral crossover group.
[y]For radial crossover versus successful radial access; [z]for radial crossover versus successful femoral access; [x]for femoral crossover versus successful femoral access.

CABG = coronary artery by-pass grafting; eGFR = estimated glomerular filtration rate; NSTE-ACS = non-ST-segment-elevation acute coronary syndrome; PCI = percutaneous coronary intervention; STEMI = ST-segment-elevation myocardial infarction; TIA = transient ischemic attack.

Adjudicated endpoints	**Radial crossover (n=183)**	**Successful radial (n=4,014)**	**Successful femoral (n=4,099)**	**Unadjusted Rate Ratio (95% CI)[y]**	**p-value[y]**	**Adjusted Rate Ratio (95% CI)[y]**	**p-value[y]**	**Unadjusted Rate Ratio (95%CI)[z]**	**p-value[z]**	**Adjusted Rate Ratio (95%CI)[z]**	**p-value[z]**
Death, myocardial infarction or stroke	25 (13.7)	344 (8.6)	407 (10.0)	1.66 (1.08-2.53)	0.018	1.25 (0.81-1.93)	0.32	1.41 (0.93-2.16)	0.10	1.17 (0.76-1.81)	0.47
Death, myocardial infarction, stroke, BARC 3 or 5	32 (17.5)	378 (9.4)	463 (11.4)	1.98 (1.35-2.89)	<0.001	1.40 (0.94-2.06)	0.090	1.63 (1.12-2.37)	0.010	1.26 (0.86-1.86)	0.24
All-cause death	7 (3.8)	59 (1.5)	84 (2.1)	2.64 (1.20-5.79)	0.011	0.32 (0.10-1.02)	0.053	1.88 (0.87-4.08)	0.10	0.68 (0.22-2.07)	0.49
Myocardial infarction	18 (9.9)	281 (7.1)	316 (7.8)	1.45 (0.88-2.39)	0.13	1.34 (0.82-2.18)	0.23	1.31 (0.80-2.15)	0.28	1.28 (0.79-2.09)	0.31
Stroke	1 (0.6)	15 (0.4)	14 (0.3)	1.48 (0.20-11.24)	0.70	1.69 (0.15-19.17)	0.67	1.62 (0.21-12.32)	0.63	1.03 (0.11-9.61)	0.97
BARC 3 or 5	8 (4.4)	57 (1.5)	96 (2.4)	3.21 (1.52-6.75)	0.001	1.28 (0.47-3.49)	0.62	1.92 (0.93-3.97)	0.073	1.10 (0.46-2.63)	0.83
BARC 3 or 5 access site-related	7 (3.9)	9 (0.2)	42 (1.1)	17.75 (6.56-47.98)	<0.001	9.65 (2.49-37.41)	0.001	3.84 (1.71-8.60)	<0.001	2.14 (0.79-5.76)	0.13
BARC 3 or 5 non-access site-related	1 (0.6)	48 (1.2)	54 (1.3)	0.46 (0.06-3.35)	0.43	0.19 (0.02-1.54)	0.11	0.42 (0.06-3.03)	0.37	0.27 (0.03-2.11)	0.21
BARC 2, 3 or 5	22 (12.1)	168 (4.2)	299 (7.4)	3.12 (1.98-4.93)	<0.001	1.80 (1.02-3.16)	0.041	1.75 (1.12-2.73)	0.013	1.26 (0.76-2.08)	0.37
BARC 2, 3 or 5 access site-related	19 (10.5)	50 (1.2)	191 (4.7)	9.06 (5.26-15.62)	<0.001	6.65 (3.60-12.26)	<0.001	2.37 (1.46-3.85)	<0.001	1.87 (1.08-3.26)	0.026
BARC 2, 3 or 5 non-access site-related	3 (1.6)	119 (3.0)	113 (2.8)	0.56 (0.18-1.75)	0.30	0.28 (0.08-1.01)	0.051	0.60 (0.19-1.88)	0.37	0.41 (0.12-1.33)	0.13

Table 2. Co-primary and main secondary adjusted and unadjusted outcomes in patients with radial crossover vs. successful radial or femoral access

Values are n (%), unless otherwise indicated.
[y]For radial crossover versus successful radial access; [z]for radial crossover versus successful femoral access.
BARC = Bleeding Academic Research Consortium; ST = stent thrombosis; TVR = target vessel revascularization.

Table 3. Co-primary and main secondary adjusted and unadjusted outcomes in patients with femoral crossover versus successful femoral access

Adjudicated endpoints	**Femoral crossover (n=108)**	**Successful femoral (n=4,099)**	**Unadjusted Rate Ratio (95% CI)**	**p-value**	**Adjusted Rate Ratio (95% CI)**	**p-value**
Death, myocardial infarction or stroke	22 (20.4)	407 (10.0)	2.17 (1.39-3.39)	<0.001	1.84 (1.18-2.87)	0.007
Death, myocardial infarction, stroke, BARC 3 or 5	23 (21.3)	463 (11.4)	1.99 (1.29-3.08)	0.001	1.69 (1.09-2.62)	0.019
All-cause death	7 (6.5)	84 (2.1)	3.24 (1.50-7.03)	0.001	3.50 (1.42-8.65)	0.006
Myocardial infarction	14 (13.3)	316 (7.8)	1.75 (1.00-3.05)	0.045	1.43 (0.83-2.44)	0.19
Stroke	2 (1.9)	14 (0.3)	5.61 (1.27-24.72)	0.010	5.31 (1.31-21.55)	0.019
BARC 3 or 5	3 (2.9)	96 (2.4)	1.21 (0.38-3.82)	0.74	1.27 (0.37-4.35)	0.69
BARC 3 or 5 access site	1 (0.9)	42 (1.1)	0.92 (0.13-6.67)	0.93	0.83 (0.09-7.29)	0.86
BARC 3 or 5 non-access site	2 (1.9)	54 (1.3)	1.44 (0.35-5.89)	0.61	1.57 (0.34-7.11)	0.56
BARC 2, 3 or 5	12 (11.3)	299 (7.4)	1.58 (0.88-2.85)	0.12	1.55 (0.82-2.92)	0.17
BARC 2, 3 or 5 access site	6 (5.6)	191 (4.7)	1.21 (0.53-2.77)	0.64	1.26 (0.51-3.14)	0.61
BARC 2, 3 or 5 non-access site	6 (5.7)	113 (2.8)	2.08 (0.91-4.76)	0.074	1.85 (0.74-4.61)	0.18

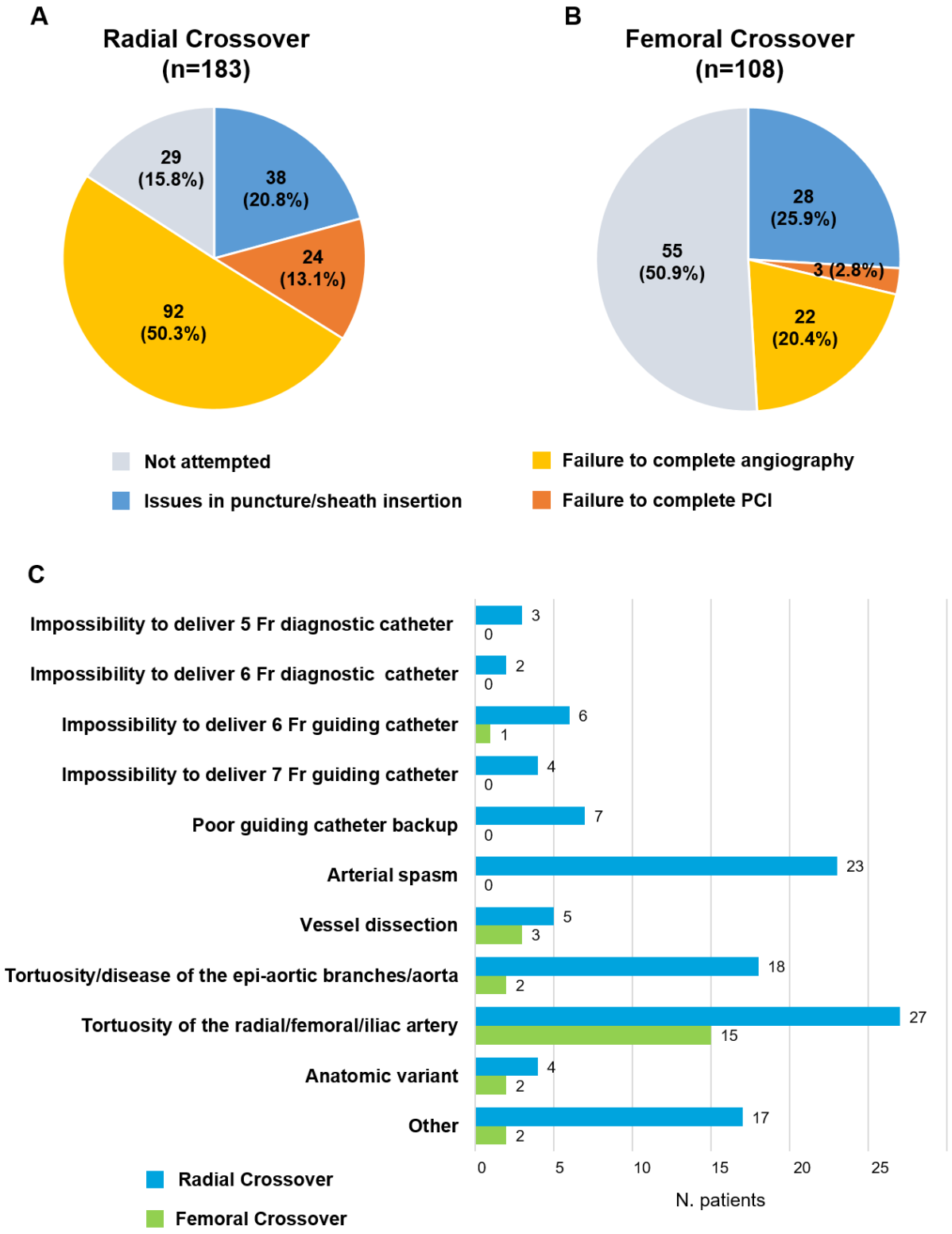
Values are n (%), unless otherwise indicated.
Rate ratios and p-values: for femoral crossover versus successful femoral access.
BARC = Bleeding Academic Research Consortium; ST = stent thrombosis; TVR = target vessel revascularization.

Table 4. Co-primary and main secondary adjusted outcomes in patients with access site crossover after initial attempts vs. successful access site

Adjudicated endpoints	**Radial crossover (n=154)**	**Successful radial (n=4,014)**	**Femoral crossover (n=53)**	**Successful femoral (n=4,099)**	**Adjusted Rate Ratio (95% CI)[y]**	**p-value[y]**	**Adjusted Rate Ratio (95%CI)[z]**	**p-value[z]**	**Adjusted Rate Ratio (95% CI)[x]**	**p-value[x]**
Death, myocardial infarction or stroke	22 (14.3)	344 (8.6)	12 (22.6)	407 (10.0)	1.32 (0.83-2.08)	0.23	1.25 (0.79-1.98)	0.34	1.78 (1.01-3.16)	0.049
Death, myocardial infarction, stroke, BARC 3 or 5	29 (18.8)	378 (9.4)	13 (24.5)	463 (11.4)	1.53 (1.02-2.30)	0.037	1.38 (0.92-2.07)	0.11	1.71 (0.97-3.01)	0.062
All-cause death	6 (3.9)	59 (1.5)	3 (5.7)	84 (2.1)	0.42 (0.12-1.47)	0.17	1.08 (0.36-3.28)	0.88	3.22 (0.96-10.73)	0.057
Myocardial infarction	16 (10.5)	281 (7.1)	9 (17.3)	316 (7.8)	1.37 (0.81-2.31)	0.23	1.30 (0.76-2.20)	0.33	1.55 (0.80-2.99)	0.19
Stroke	1 (0.7)	15 (0.4)	1 (2.0)	14 (0.3)	1.83 (0.15-21.82)	0.63	1.41 (0.16-12.55)	0.75	4.24 (0.67-26.71)	0.12
BARC 3 or 5	8 (5.3)	57 (1.5)	2 (3.8)	96 (2.4)	1.81 (0.68-4.80)	0.23	1.34 (0.55-3.27)	0.52	1.50 (0.33-6.80)	0.60
BARC 3 or 5 access site	7 (4.6)	9 (0.2)	1 (1.9)	42 (1.1)	13.16 (3.73-46.47)	0.0001	2.56 (0.92-7.12)	0.071	1.57 (0.17-14.19)	0.68
BARC 3 or 5 non-access site	1 (0.7)	48 (1.2)	1 (1.9)	54 (1.3)	0.25 (0.03-2.06)	0.19	0.34 (0.04-2.70)	0.30	1.37 (0.17-11.15)	0.77
BARC 2, 3 or 5	21 (13.8)	168 (4.2)	8 (15.3)	299 (7.4)	2.01 (1.13-3.57)	0.017	1.39 (0.82-2.35)	0.22	2.39 (1.18-4.88)	0.016
BARC 2, 3 or 5 access site	19 (12.5)	50 (1.2)	5 (9.5)	191 (4.7)	7.76 (4.19-14.36)	<0.0001	2.20 (1.25-3.87)	0.0061	2.50 (0.98-6.37)	0.054
BARC 2, 3 or 5 non-access site	2 (1.3)	119 (3.0)	3 (5.7)	113 (2.8)	0.21 (0.05-1.01)	0.051	0.31 (0.07-1.30)	0.10	1.94 (0.62-6.07)	0.25

Values are n (%), unless otherwise indicated.
[y]For radial crossover after initial attempts versus successful radial access; [z]for radial crossover after initial attempts versus successful femoral access; [x]for femoral crossover after initial attempts versus successful femoral access.
BARC = Bleeding Academic Research Consortium; GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator; ST = stent thrombosis; TIMI = Thrombolysis in Myocardial Infarction; TVR = target vessel revascularization.

Figure 1


A
Radial Crossover
(n=183)
29
(15.8%)
38
(20.8%)
24
(13.1%)
92
(50.3%)
B
Femoral Crossover
(n=108)
28
(25.9%)
55
(50.9%)
3 (2.8%)
22
(20.4%)
Not attempted
Issues in puncture/sheath insertion
Failure to complete angiography
Failure to complete PCI
C
Impossibility to deliver 5 Fr diagnostic catheter
Impossibility to deliver 6 Fr diagnostic catheter
Impossibility to deliver 6 Fr guiding catheter
Impossibility to deliver 7 Fr guiding catheter
Poor guiding catheter backup
Arterial spasm
Vessel dissection
Tortuosity/disease of the epi-aortic branches/aorta
Tortuosity of the radial/femoral/iliac artery
Anatomic variant
Other
3
0
2
0
6
1
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23
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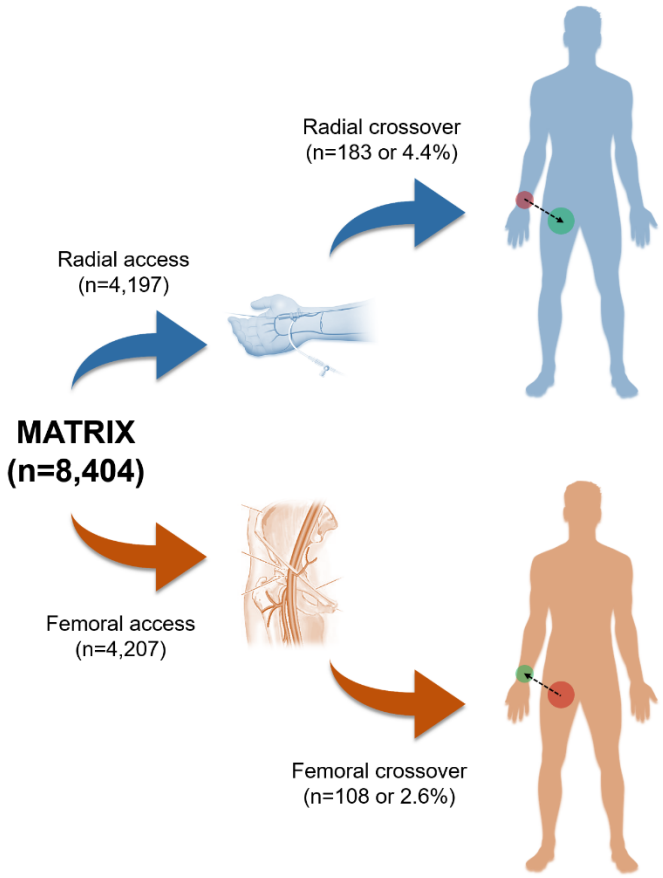
N. patients
Radial Crossover
Femoral Crossover

Central Illustration

A



B

Outcomes	N. of events (%)		Multivariate Adjusted Rate Ratio (95% Confidence Interval)	p-value
Radial crossover vs. Successful radial access				
MACE	25 (13.7%)	344 (8.6%)	1.25 (0.81-1.93)	0.32
NACE	32 (17.5%)	378 (9.4%)	1.40 (0.94-2.06)	0.09
BARC 3 or 5	8 (4.4%)	57 (1.5%)	1.28 (0.47-3.49)	0.62
BARC 3 or 5 access site	7 (3.9%)	9 (0.2%)	9.65 (2.49-37.41)	0.001
BARC 2, 3 or 5	22 (12.1%)	168 (4.2%)	1.80 (1.02-3.16)	0.041
BARC 2, 3 or 5 access site	19 (10.5%)	50 (1.2%)	6.65 (3.60-12.26)	<0.001
Radial crossover vs. Successful femoral access				
MACE	25 (13.7%)	407 (10.0%)	1.17 (0.76-1.81)	0.47
NACE	32 (17.5%)	463 (11.4%)	1.26 (0.86-1.86)	0.24
BARC 3 or 5	8 (4.4%)	96 (2.4%)	1.10 (0.46-2.63)	0.83
BARC 3 or 5 access site	7 (3.9%)	42 (1.1%)	2.14 (0.79-5.76)	0.13
BARC 2, 3 or 5	22 (12.1%)	299 (7.4%)	1.26 (0.76-2.08)	0.37
BARC 2, 3 or 5 access site	19 (10.5%)	191 (4.7%)	1.87 (1.08-3.26)	0.026
Femoral crossover vs. Successful femoral access				
MACE	22 (20.4%)	407 (10.0%)	1.84 (1.18-2.87)	0.007
NACE	23 (21.3%)	463 (11.4%)	1.69 (1.09-2.62)	0.019
BARC 3 or 5	3 (2.9%)	96 (2.4%)	1.27 (0.37-4.35)	0.69
BARC 3 or 5 access site	1 (0.9%)	42 (1.1%)	0.83 (0.09-7.29)	0.86
BARC 2, 3 or 5	12 (11.3%)	299 (7.4%)	1.55 (0.82-2.92)	0.17
BARC 2, 3 or 5 access site	6 (5.6%)	191 (4.7%)	1.26 (0.51-3.14)	0.61