POINT-OF-VIEW

Efficacy of Radial Versus Femoral Access in the Acute Coronary Syndrome

Is it the Operator or the Operation That Matters?

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ABSTRACT

In the recently published MATRIX (Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX) trial, the use of transradial access (TRA) compared to transfemoral access (TFA) during percutaneous coronary intervention (PCI) for acute coronary syndrome (ACS) was associated with a reduction in net adverse cardiovascular events. However, the results of MATRIX must be interpreted with caution due to several limitations including the strong modulating effect of operator/center experience on the relative efficacy of TRA and the inclusion of 2 distinct patient populations (ST-segment elevation and non-ST-segment elevation ACS). Therefore, although important, the results of MATRIX have strong limitations and are not sufficient to definitively identify an approach of choice during PCI for ACS. Further research is needed before strong, evidence-based recommendations regarding the approach of choice during PCI for ACS can be made. (J Am Coll Cardiol Intv 2015;8:1405–9) © 2015 by the American College of Cardiology Foundation.

A recently published, large, randomized study, MATRIX (Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX) (1), compared transradial access (TRA) to transfemoral access (TFA) in patients presenting with acute coronary syndromes (ACS) who were referred for percutaneous coronary intervention (PCI). The results of this trial have been interpreted to suggest that TRA is superior to TFA in reducing net adverse clinical events (NACE) through a reduction of bleeding and mortality. This conclusion could significantly affect our practice guidelines and lead to a strong recommendation that the approach of choice for PCI in ACS is radial rather than femoral. Hence, this trial has significant implications for both PCI centers and interventionalists, and it could have an effect on medical practice and education. However, the MATRIX trial has serious shortcomings that need to be considered.

The MATRIX trial randomly assigned 8,404 ACS patients to TRA (n = 4,197) or TFA (n = 4,207) to compare clinical outcomes in patients referred for coronary angiography and PCI (1). The study was designed with 2 30-day coprimary endpoints: 1) major adverse cardiovascular events (MACE), defined as all-cause mortality, myocardial infarction, or stroke; and 2) NACE, defined as major bleeding unrelated to coronary artery bypass graft surgery or major adverse cardiovascular events. Major bleeding was classified according to the Bleeding Academic Research Consortium (2). Because of multiple comparisons, the 2-sided α was pre-specified at 0.025 for each primary endpoint. MACE was recorded in 8.8% of patients assigned to TRA and in 10.3% of patients assigned to TFA (p = 0.03); this was interpreted as nonsignificant. However, the rate of NACE was significantly lower in patients assigned to TRA compared to TFA (9.7% vs. 11.7%, respectively; p = 0.009); a difference said to be driven by major bleeding (1.6% vs. 2.3%; p = 0.013)

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndromes(s)

MACE = major adverse cardiovascular events(s)

NACE = net adverse clinical events(s)

NSTE-ACS = non-ST-segment elevation acute coronary syndrome

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

TFA = transfemoral access

TRA = transradial access

and all-cause mortality (1.6% vs. 2.2%; p = 0.045). The authors suggest that the benefits associated with implementation of TRA for the treatment of ACS "might be especially relevant for countries such as the USA where use of the radial approach is currently uncommon" (3). However, a critical appraisal of the MATRIX trial's results will cast a word of caution before accepting the authors' conclusions.

First, it is quite clear that the outcomes were dependent upon the center's experience at performing PCI. A center's experience is determined by its access preference (i.e., the proportion of TRA vs. TFA) and by its annual PCI volume; in addition, the experience levels of the operator, the catheterization team, as well as the team monitoring the patient after the PCI all contribute to the overall experience of the center. The MATRIX study divided patients into 3 groups based on the participating center's proportion of radial PCIs: "low" (14.9% to 64.4%), intermediate (65.4% to 79.0%), and high (80.0% to 98.0%). The results of this stratified analysis are shown in **Figure 1**. As noted by the authors, and illustrated in the figure, there is a strong interaction between the randomized mode of access and the center's proportion of radial procedures for both MACE (p = 0.0048) and NACE (p = 0.0048). This interaction is so strong that to compare TRA and TFA without taking the center's experience into consideration would be an oversight.

In fact, the only time TRA is significantly better than TFA occurs when the results are considered only for centers with a high proportion (80.0% to 98.0%) of PCIs done using TRA. There is no difference even when the proportion of TRA is as high as 79% (14.9% to 79.0%). Although the labels "low," "intermediate," and "high" are used, more appropriate labels would be "intermediate," "high," and "very high," respectively, given the percentages that they represent. It is only in the "very high" group that there is a difference favoring TRA, and it occurs in centers with essentially no or very limited TFA experience. One could argue that operators in these centers have optimal TRA skills that enable the benefit of TRA to be more evident; however, it remains unexplained why the absolute rates of MACE and NACE in the TRA group were unexpectedly higher in centers with a "high" proportion of radial procedures compared with those in the "low" and "intermediate" centers. Furthermore, in the "high" radial proportion centers, the rates of MACE and NACE in the TFA group were excessive, 15.5% and 17.1%, respectively, compared

with the rates reported for centers with a "low" or "intermediate" proportion of radial procedures. Notably, these results did not appear to be linked to the overall annual PCI volume.

An alternative explanation is that centers performing PCI almost exclusively by TRA have limited contemporary experience with TFA and consequently have more complications. Randomizing patients to receive TFA in centers with very little experience would obviously be detrimental for outcomes in the TFA group. With such an interaction, one needs to take center experience into consideration either by interpreting the results within levels of center experience or by statistically adjusting the results by including center experience as a covariate in any modeling. Hence, the analysis of this trial may have actually assessed center experience rather than the use of the access site itself, and this may very well account for the measured differences in clinical outcomes.

Second, the MATRIX trial had a complex design that attempted to resolve many questions by incorporating multiple comparisons: 1) TRA versus TFA; 2) bivalirudin monotherapy versus unfractionated heparin plus provisional glycoprotein platelet inhibitors (GPIs); and 3) short- versus long-term administration of bivalirudin. This approach likely introduced multiple interventions that could potentially distort the interpretation of the results.

In light of the multiple comparisons, the alpha for significance was set at 0.025 for the 2 primary outcomes (4). However, the p value was reset at 0.05 for the individual components of MACE and NACE. One could argue that, given the 4 components of NACE, a Bonferroni-corrected alpha of 0.0125 should have been used. This argument coincides with many authors' recommendations, most recently by Rauch et al. (5), that strategies such as the Bonferroni-Holm's approach should be used when evaluating the components of a composite outcome. In so doing, the difference reported for mortality in the MATRIX trial would not have been statistically significant.

Third, the MATRIX trial enrolled patients presenting with ST-segment elevation myocardial infarction (STEMI) and non–ST-segment elevation acute coronary syndrome (NSTE-ACS). Of note, the MATRIX trial did not stratify STEMI and NSTE-ACS in the randomization process (4). Without including stratification into the study design, one needs to exercise caution in the interpretation of the results in these subgroups as the 2 clinical entities differ considerably in pathophysiology and management options, thus possibly skewing the results. Notable differences between both patient populations include: 1) the acuity level; 2) the importance of time to reperfusion;