In fact, in the 2 most contemporary risk scores developed for long-term thrombotic and bleeding risk prediction in DES-treated patients on antiplatelet therapies (4,5), female sex did not emerge as an independent correlate of bleeding events. Given the safety and efficacy of new-generation DES and the availability of novel and more potent $P2Y_{12}$ inhibitors, we should strive to provide the best available therapies for high-risk women with coronary artery disease.

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# Validity of Randomized Trials Comparing Radial Versus Femoral Access in Acute Coronary Syndrome

Andò and Capodanno (1) concluded by meta-analysis of randomized controlled trials (RCTs) that in patients with acute coronary syndrome (ACS), transradial access (TRA) improves mortality and major adverse cardiovascular event (MACE) rates compared to transfemoral access (TFA). They also point out that during sensitivity analysis, removing the MATRIX (Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX) trial data causes the summary results for MACE to become nonsignificant. Similarly, mortality reduction with TRA becomes statistically and clinically significant only after data from the MATRIX trial was included. These observations suggest that their conclusion was driven predominantly by the MATRIX trial data. However, they failed to point out the major limitations of the MATRIX trial, which potentially limit the generalizability of their meta-analysis (2,3).

In the MATRIX trial, the reported MACE rates were much higher in the TFA arms than was seen in other related randomized trials (2). It also showed significantly higher rates of MACE, net adverse clinical events, and mortality in the femoral group of the high radial volume centers compared with other centers (2,4). Thus, the significant difference in the outcomes between TFA and TRA in the MATRIX trial seems to be caused by the poor outcomes in the femoral group rather than the benefits of radial access (2,4).

Furthermore, a recent meta-analysis of RCTs showed that in ACS patients undergoing percutaneous coronary intervention, TFA by radial experts, compared to nonexperts, is associated with higher MACE and mortality rates (5). It is well known that the volume of patients handled by hospitals and operators correlates with outcomes. Radial experts performing in high radial volume centers are considered to be low femoral volume access centers, and this could explain the high MACE and mortality rates in the femoral group (2). This suggests that the experience of the center and operators, rather than the access site, determines outcomes.

Therefore, all the RCTs in this field must be scrutinized as to whether they are true RCTs comparing groups only by access type. In RCTs, all intervention groups must be treated identically except for the experimental treatment, but in the RCTs used here, a majority of the procedures were performed by radial experts in high radial volume centers. High radial volume centers were low-volume centers for TFA, thus leading to higher MACE and mortality rates in the TFA arms and introducing significant bias favoring the TRA arms (5). Thus, not only is the external validity (generalizability) of these RCTs an issue, but also internal

validity is a major concern. These matters need further investigation before American guidelines are changed, making TRA the default access for all patients with ACS (as recommend by those who performed this meta-analysis).

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## REPLY: Validity of Randomized Trials Comparing Radial Versus Femoral Access in Acute Coronary Syndrome

We thank Drs. Shah and Ahmed for their interest in our meta-analysis of randomized clinical trials of radial versus femoral access in patients with acute coronary syndromes (ACS) undergoing invasive management, suggesting that the publication of the MATRIX (Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX) trial has been historically instrumental in consolidating the superiority of radial access for mortality and major adverse cardiac or cerebrovascular events (1).

To undermine the conclusions of our meta-analysis, Shah and Ahmed point out what they consider to be a critical limitation of the MATRIX trial, namely the poor outcomes of patients undergoing femoral access in centers with >80% of radial procedures (2). Valgimigli et al. have extensively given valid arguments against this oversimplified perspective of the MATRIX trial results in a reply to another similar letter by Shad and colleagues sent to *The Lancet* (3) and in a recent debate here in *JACC: Cardiovascular Interventions* (4). Indeed, deep diving into one single study as done by Shah and Ahmed goes beyond the scope of a meta-analysis, which is aimed at appraising the quality of included studies, pooling their results to look for overall effects, and assessing inconsistency.

Then, as far as our study is concerned, the following considerations apply. First, we reported that after inclusion of the MATRIX trial, the z-curve of the trial sequential analysis crossed the monitoring boundary indicating that a new trial is unlikely to change the firm evidence now supporting the mortality benefit of radial access. On this background, Shad and Ahmed should note that the conventional statistical significance boundary for mortality was crossed well before the MATRIX trial. Second, the loss of statistical significance for major adverse cardiac or cerebrovascular events when the MATRIX trial is removed (with a p value of 0.08) did not result in a significant deviation of the treatment effect of radial access (0.85 instead of 0.86) indicating that MATRIX just added the necessary power to make this difference significant, but did not change the direction of the point estimate. Third, the heterogeneity ($I^2$) for all these outcomes was zero. Having said that, we believe that debating p values for subgroup and sensitivity analyses of single endpoints is specious and sounds artificial in view of the established benefit of radial access in reducing major bleeding—a non-negligible complication in the setting of ACS—as noted in other meta-analyses and well before the MATRIX trial.

In their conclusion, Shah and Ahmed request more studies before the American guidelines align with those from Europe where radial access is now considered a Class I A for patients with ACS. In particular, they deny our (and the Editorialist's) request to make radial access a "default approach" in ACS. The word *default* does not imply the use of radial access in 100% of the procedures. Indeed, structural and some coronary procedures still are, and still will be, performed through the femoral route. Simply, acquiring skills in radial procedures—while maintaining proficiency in both vascular access sites—is becoming more and more essential in the interventionalist's armamentarium, as part of a bleeding avoidance strategy for improving patient outcomes.