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.

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