large cohort (n = 10,241) to help us improve our understanding of the outcomes of percutaneous coronary intervention in women. I was particularly encouraged to see improved results for newer drug-eluting stent platforms in terms of reducing major adverse cardiac events (defined as the composite of all-cause mortality, myocardial infarction, and target lesion revascularization at 3 years).

However, one of the concerns when treating women is the risk for bleeding, particularly when faced with patients who may be older and of relatively low weight compared with their male counterparts. This is reflected in bleeding risk predictor scores, which include female sex as an important predictive factor (2,3). Indeed, female sex carries even more weight in these validated scores than baseline anemia. Importantly, previous work suggests that even if data are adjusted to take into account age, body mass index, and type of antithrombotic therapy, female sex remains an independent predictor of bleeding (4). Furthermore, the investigators quite correctly state that women are at increased risk for problems such as access-site complications, but they do not provide us with the rate of occurrence of such events in their population.

As the investigators are well aware, the occurrence of bleeding after coronary intervention increases the risk for death and, importantly, is associated with not insignificant morbidity (5). This is important because of the effect on quality of life as well as the cost implications of a prolonged hospital stay. It is therefore difficult to fully appreciate the results presented in this present study when taken in such isolation. The inclusion of safety information about major adverse bleeding events should be described as a fundamental part of studies of this nature.

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REPLY: Drug-Eluting Stents Are Effective in Women

Only Part of the Story?

We appreciate the interest of Dr. Hoye in our study investigating the efficacy and safety of new-generation drug-eluting stents (DES) versus early-generation DES in women undergoing complex percutaneous coronary intervention (PCI) (1). Dr. Hoye's point is very well taken, as in the past, female sex proved to be strongly associated with increased risk for periprocedural vascular and bleeding complications (2). Unfortunately, such adverse events were not captured in the patient-level pooled dataset of the 26 randomized controlled trials included in this collaborative analysis. However, although the rates of vascular and bleeding complications are of concern in women undergoing coronary and structural percutaneous interventions, some considerations must be made.

First, not only have women been previously underrepresented in randomized controlled trials of cardiovascular devices, but they also constitute an underdiagnosed, undertreated, and underresearched population with considerable room for improvement (3). That being said, our findings supporting improved efficacy and safety of new-generation DES even in highly complex coronary anatomies is reassuring and should encourage physicians to treat women with high-risk anatomy with PCI, especially when they are not suitable for surgical revascularization.

Second, we should differentiate between in-hospital and out-of-hospital bleeding complications after PCI with DES. Although female sex was demonstrated to be among the strongest risk factors for periprocedural access-related and nonaccess-related hemorrhagic complications after PCI, its association with post-discharge bleeding is uncertain.

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