REPLY: The Hidden Players

We appreciate the comments by Dr. Mahmoud and colleagues about our study. They argued that heterogeneity for major bleeding may have confounded our analysis due to an imbalanced use of radial access and glycoprotein IIb/IIIa inhibitors (GPI) between the unfractionated heparin (UFH) and bivalirudin groups. First, as we noted in our original paper (1), the heterogeneity appeared to originate from the single-center study (i.e., How Effective Are Antithrombotic Therapies in Primary Percutaneous Coronary Intervention [HEAT PPCI]). Once this study was removed from our sensitivity analysis, no significant heterogeneity ($p = 0.123$) remained among the 4 remaining (multicenter) trials. It is well known that a single-center study is typically an outlier when combined with multicenter trials in a meta-analysis (2). Therefore, it is strongly recommended that meta-analysts perform sensitivity analyses to demonstrate how their conclusions might be affected by the exclusion of single-center trials (2).

Second, the primary focus of our paper was to evaluate the effect of prolonged bivalirudin infusion on major bleeding and acute stent thrombosis. Prolonged bivalirudin infusion at the full percutaneous coronary intervention (PCI) dose was used only in the MATRIX (Minimizing Adverse Hemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox), EUROMAX (European Ambulance Acute Coronary Syndrome Angiography Trial), and BRIGHT (Bivalirudin in Acute Myocardial Infarction vs Heparin and GPI Plus Heparin Trial) trials. No heterogeneity was found among these trials ($Q = 3.1$; $df = 3$; $p = 0.374$; $I^2 = 3$) for the prolonged infusion subgroup analysis. Radial access was used in the same number of patients in both the bivalirudin and UFH groups in these trials. In addition, the MATRIX trial investigators found no evidence of interaction between access route and allocation to the bivalirudin or UFH groups for major bleeding (p for interaction ≥0.64) (3). In the EUROMAX trial, bivalirudin was associated with a significantly lower rate of major bleeding (odds ratio: 0.44; 95% confidence interval: 0.24 to 0.82), even when compared with UFH without routine GPI (4). Similarly, in the BRIGHT trial, bleeding (1 of the primary endpoints) was reduced with bivalirudin compared with UFH alone and UFH with GPI (4.1%, 7.5%, and 12.3%, respectively; $p < 0.001$). Furthermore, during sensitivity analysis, removing the BRIGHT-UFH+GPI data did not change our summary result for major bleeding (risk ratio: 0.31; 95% CI: 0.15 to 0.63; $p = 0.001$). Finally, current guidelines recommend a 70 to 100 U/kg bolus of UFH without GPI or a 50 to 70 U/kg bolus of UFH with GPI for primary PCI, which were used in these trials.

Thus, it is very unlikely that our conclusion about the effect of prolonged bivalirudin infusion on major bleeding was confounded by these factors. However, as we noted in our original paper, access to patient-level data would enable multivariate analysis, which would markedly strengthen this analysis.

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Optimal Medical Therapy in the Prognosis of Coronary Artery Disease

We read with great interest the paper by Migliorini et al. (1). In their article, the investigators reported that there is no impact of high anatomic complexity as defined by a SYNTAX score of ≥33 on clinical outcomes after percutaneous coronary intervention (PCI) in patients with unprotected left main disease. This finding may indicate the superiority of everolimus-eluting stents (EES) over that of first-generation drug-eluting stents, and EES may be associated with better angiographic and clinical results. However, there are still some points that need to be explained. Higher SYNTAX score is a well-known prognostic

factor in patients with unprotected left main disease undergoing revascularization (2). Also, PCI does not reduce the mortality and adverse events in the presence of optimal medical therapy in patients with stable coronary artery disease (3). Hence, optimal medical therapy including statins, beta-blockers, and angiotensin-converting enzyme inhibitors is essential to reduce adverse events and mortality in patients with coronary artery disease undergoing revascularization (4). In this sense, significant differences in the treatment with these medications may affect the prognosis independent of PCI and SYNTAX score. The investigators should clearly state the incidence of treatment with these medications for each group, respectively, to clarify the prognostic value of EES and high SYNTAX score.

Additionally, in the Migliorini et al. (1) study, there are no data regarding comparison of incidence of patients treated with prasugrel for the groups. In the presence of acute coronary syndrome, in particular, ST-segment elevation myocardial infarction, treatment with prasugrel significantly reduces the adverse events independently compared with treatment with clopidogrel (4,5). Therefore, type of dual antiplatelet therapy may effect the prognosis and clinical events independent of stent type and SYNTAX score.

PCI with EES may lead an improvement in clinical results. However, optimal medical therapy remains the key point in the treatment of a population with coronary artery disease. Treatment with optimal medical therapy including statins, beta-blockers, and angiotensin-converting enzyme inhibitors and type of dual antiplatelet therapy should be taken into consideration to clarify the prognostic significance of EES and SYNTAX score.

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REPLY: Optimal Medical Therapy in the Prognosis of Coronary Artery Disease

We thank Drs. Eyuboglu and Kucuk for their interest in our study.

The aim of our study was to test if high SYNTAX (SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery) score may be considered valid in the new-generation everolimus-eluting stent era in patients with unprotected left main disease (ULMD) to guide the optimal revascularization modality (1). Our data show that SYNTAX score is not predictive of cardiac mortality in patients with ULMD treated with everolimus-eluting stent. However, as outlined in the accompanying editorial, these results were achieved in a center with high chronic total occlusion percutaneous coronary intervention (PCI) success rate, high rate of complete revascularization, and routine use of intravascular ultrasound and evidence-based techniques such as bifurcation lesion treatment (2).

Drs. Eyuboglu and Kucuk refer to the PCI results of the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive druG Evaluation) trial (3). In the COURAGE trial bare-metal stents were used, and our study population is very different from the low-risk and low coronary anatomy complexity population of the COURAGE trial. With regard to medical therapy, all patients were on optimal medical therapy according to the American College of Cardiology/American Heart Association guidelines. Overall, the rate of statin use was 98%, beta-blockers 63%, and angiotensin-converting enzyme inhibitors 82%, and there were no differences between groups in the use of these drugs. Regarding the antiplatelet therapy, the use of prasugrel was very high according to the results of 2 previous studies showing a strong benefit of prasugrel as compared with clopidogrel in ULMD PCI and in clopidogrel nonresponders (4,5). Prasugrel was used in 85% of patients, while all patients treated with clopidogrel were clopidogrel