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Reply to Letter to the Editor: "What Is the Optimal Antiplatelet Therapy in Type 2 Diabetes Mellitus Patients with Small Diameter Stents?"

LETTER TO THE EDITOR
REPLY

To the Editor,

The authors of the letter titled "What Is the Optimal Antiplatelet Therapy in Type 2 Diabetes Mellitus Patients with Small Diameter Stents?"[1] are gratefully acknowledged for their thoughtful and constructive feedback on the published article in the *Anatolian Journal of Cardiology*.[2] The opportunity to respond to the points raised and further clarify the findings is appreciated.

The letter appropriately references the PLATO trial[3] and its post hoc analysis in diabetes mellitus and CKD populations. As noted in the discussion, while ticagrelor demonstrated ischemic benefits in broader cohorts, including those with CKD. But PLATO analysis did not focus on the population with small-diameter stents. However, a signal toward benefit in the CKD subgroup with small-diameter stents was observed, which aligns partially with prior evidence. In a sub-study of the TICO randomized trial (clinicaltrials.gov identifier: NCT02494895), patients with small vessel disease showed a higher target lesion failure rate than those with non-small vessel disease (2.9% vs. 1.0%, log-rank $P < .001$), despite both groups receiving ticagrelor. Specifically, patients with small vessel disease experienced a higher incidence of cardiac death (1.5% vs. 0.4%, P value .002) and stent thrombosis, underscoring the persistent risk associated with small-vessel PCI even under potent antiplatelet therapy.[4] The lack of reduction in acute stent thrombosis with ticagrelor compared to clopidogrel in the PLATO trial aligns with observations from the TRITON-TIMI 38 trial,[5] where prasugrel also failed to demonstrate a significant benefit in early stent thrombosis (within 30 days) despite its potent antiplatelet effects. This suggests that factors beyond P2Y12 inhibition (e.g., procedural, stent-related, or thrombotic milieu) may influence early stent thrombosis risk.[6] In a propensity score-matched retrospective study of 1230 patients with well-balanced clinical characteristics, no significant difference in ischemic outcomes was observed between ticagrelor and clopidogrel in the IVUS-guided PCI subgroup, probably due to the precise implantation of IVUS.[7]

We agree that pharmacogenomic variability (e.g., CYP2C19 loss-of-function alleles affecting clopidogrel efficacy) is a critical factor in antiplatelet therapy. While this study did not genotype participants, prior evidence showing that ticagrelor's non-CYP2C19-dependent metabolism may offer more consistent platelet inhibition in diabetes was referenced.[8] However, as noted, the cohort's racial composition (predominantly Middle Eastern) may differ from PLATO's Western population. While racial and ethnic variations in platelet reactivity and drug metabolism are acknowledged in the literature, it is concurred that any related claims should be substantiated with pharmacological and genetic data, which were beyond the scope of this study. Larger multicenter studies stratified by race and incorporating pharmacogenetic profiling to further explore these differences are recommended.

In this study, 82% of follow-ups were conducted via clinic visits, with telephone contact (18%) reserved for patients with logistical barriers. All endpoint events

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(e.g., bleeding, MACE) were cross-verified with hospital records or physician reports. The exclusion of patients aged ≥70 years may underestimate bleeding risks associated with ticagrelor in older populations, as demonstrated in the POPular AGE trial.[9] Future studies should prioritize inclusive enrollment of elderly patients. The findings align with Asian studies showing comparable ischemic outcomes between ticagrelor and clopidogrel in small diameter stents. This underscores the need for region-specific guidelines considering genetic, clinical, and lifestyle factors.

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