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Reply to the Letter to the Editor: "Risk Trajectory and Right Ventricular Adaptation in Selexipag-Based Triple Therapy for Pulmonary Arterial Hypertension"

LETTER TO THE EDITOR REPLY

To the Editor,

We read with great interest the Letter to the Editor entitled "Risk Trajectory and Right Ventricular Adaptation in Selexipag-Based Triple Therapy for Pulmonary Arterial Hypertension"[1] on our manuscript published in the *Anatolian Journal of Cardiology* evaluating the durability of selexipag-based sequential triple combination therapy in pulmonary arterial hypertension (PAH).[2]

We thank the authors[1] for their thoughtful and constructive comments regarding our study on longitudinal evaluation of selexipag-based sequential triple therapy and their emphasis on right ventricular–pulmonary arterial (RV–PA) coupling dynamics.

We agree that signals suggesting a trend for attenuation of risk reduction after the first year deserve careful interpretation. Given the single-center data reflecting real-world longitudinal dynamics rather than randomized controlled trial conditions and decreasing sample size at later time points, attenuation should be interpreted cautiously. However, this pattern likely reflects the natural history of PAH rather than loss of therapeutic effect. Importantly, sustained reductions in N-terminal pro-brain natriuretic peptide levels and relative preservation of tricuspid annular plane systolic excursion (TAPSE) in our cohort suggest maintained RV adaptive reserve despite progressive pulmonary vascular load. This apparent divergence between RV performance markers and pulmonary arterial pressures may reflect dynamic alterations in RV-PA coupling rather than simple attenuation of therapeutic efficacy.[3,4]As discussed before, RV adaptation is not linearly related to afterload but depends on coupling efficiency and contractile reserve.[3] Accordingly, composite risk regression over time may capture evolving RV–pulmonary vascular interactions that are not fully represented by globally utilized multiparametric risk scores. Clinically, reliance on a single risk trajectory may obscure phenotype-specific signals that could inform earlier, individualized therapeutic escalation, suggesting ongoing RV compensation despite progressive vascular remodeling.

Our survival analyses further reinforce the primacy of baseline biological risk over treatment intensity, as stated by authors. Moreover, our observation that achieved selexipag dose was not independently associated with mortality should not be interpreted as a lack of dose relevance, but rather as a reflection of individualized titration strategies based on tolerability and clinical response in the context of prostacyclin pathway pharmacology, where tolerability-driven dose escalations may not reliably represent effective receptor occupation.[5]

While early risk reclassification did not yield strong long-term survival discrimination in our cohort, we believe early improvement remains clinically meaningful, particularly for symptom burden and functional status. We agree that

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lower risk status assessed by REVEAL Lite 2.0 at the time of selexipag initiation on the background double combination therapy predicted the risk status attained at final assessment. This finding aligns with the Prostacyclin (PGI) Receptor Agonist in Pulmonary Arterial Hypertension (GRIPHON) study paradigm, suggesting that earlier escalation to triple therapy within 6 months, before progression to advanced risk strata, may allow more durable stabilization of disease course. [6] Thus, rather than contradicting the importance of baseline risk, our data reinforce the concept that risk at the time of therapeutic escalation is a modifiable determinant when intervention occurs sufficiently early.

We acknowledge that congenital heart disease–associated PAH represents a distinct adaptive phenotype. Subgroup analyses were limited by sample size; however, we agree that etiology-specific modeling represents an important direction for future investigation.

We appreciate the authors again for highlighting the importance of RV–PA coupling and phenotype-aware risk interpretation. We agree that tailored management strategies with the incorporation of serial coupling metrics for an extended observation period may enhance future longitudinal risk modeling strategies in this setting.

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