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Risk Trajectory and Right Ventricular Adaptation in Selexipag-Based Triple Therapy for Pulmonary Arterial Hypertension

LETTER TO THE EDITOR

To the Editor,

We read with great interest the study by Tokgöz et al[1] evaluating the durability of selexipag-based sequential triple combination therapy in pulmonary arterial hypertension.[1] The authors should be acknowledged for their longitudinal design, extended follow-up, and the parallel application of multiple validated multiparametric risk frameworks. The integration of clinical status, echocardiography, invasive hemodynamics, and Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management–based tools allows a nuanced examination of risk evolution beyond isolated surrogate endpoints. However, certain aspects merit further discussion.

The longitudinal data reveal a pattern in which early improvements across functional class, 6-minute walk distance, echocardiographic indices, and composite risk scores are followed by gradual attenuation after the first year. This attenuation does not occur uniformly across physiological domains. Sustained reductions in N-terminal pro-brain natriuretic peptide levels and relative preservation of tricuspid annular plane systolic excursion suggest continued right ventricular adaptive capacity despite rising pulmonary arterial pressures. Such divergence implies that composite risk regression may reflect evolving ventricular–vascular uncoupling rather than simple loss of therapeutic effect.[2] Clinically, collapsing these trajectories into a single risk narrative may obscure opportunities for earlier phenotype-directed escalation.

Survival analyses further reinforce the primacy of baseline biological risk over treatment intensity. Outcomes tracked consistently with baseline Swedish Pulmonary Arterial Hypertension Registry, Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management, and echocardiography-derived risk profiles, while achieved selexipag dose showed no independent association with mortality. This finding should be interpreted in the context of prostacyclin pathway pharmacology, where tolerability-driven dose ceilings do not reliably correspond to effective receptor engagement.[3] In practice, these data favor risk-guided strategy over dose-centric escalation and caution against equating higher nominal dosing with superior long-term benefit.

The limited prognostic separation afforded by early follow-up risk reassessment adds further complexity. Although several patients transitioned to lower-risk categories within the first year, this reclassification did not translate into sustained survival discrimination. Reliance on short-term risk improvement as evidence of disease stabilization may therefore delay recognition of ongoing pathobiological progression and postpone necessary therapeutic recalibration. The substantial representation of congenital heart disease–associated pulmonary arterial hypertension further contextualizes the findings. Differences in right ventricular remodeling and adaptive reserve across etiologies may contribute to the dissociation between functional gains and longer-term outcomes,[4] emphasizing the need for etiology-aware interpretation of aggregate risk metrics.

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Taken together, the data indicate that early improvements with selexipag-based triple therapy do not uniformly translate into durable risk modification and that baseline risk status remains the dominant determinant of prognosis. We commend the authors for their rigorous multiparametric evaluation and extended observation period. Incorporation of serial right ventricular–pulmonary arterial coupling metrics may help refine timing and selection of subsequent therapeutic strategies in pulmonary arterial hypertension.

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