hyperproliferative, apoptosis-resistant, and proinflammatory phenotype of microvascular endothelial cells and smooth muscle cells isolated from patients with pulmonary arterial hypertension (PAH). A previous study demonstrated that low-plasma high-density lipoprotein cholesterol (HDL-C) was associated with higher mortality and clinical worsening outcomes, including hospitalization and lung transplantation in the patients with PAH (2). Administration of RVX-208 in the patients with coronary artery disease for 12 weeks was significantly associated with modulation of lipids metabolism, including increases in HDL-C level and concentration of large HDL particles (3). Hence, we considered whether, first, the change of HDL-C would be one feasible clinical biomarker to reflect the responsiveness of drugs or prognostic value in the patients with PAH. For example, the enhancement of HDL-C in plasma through RVX-208 treatment would improve the clinical outcomes in patients with PAH, and second, based on the beneficial effects of RVX-208 on the amelioration of vascular remodeling, pulmonary hemodynamics, and right ventricle in different preclinical models of PAH (1), the casual link among these observed outcomes, efficacy of RVX-208 therapy, and the change of HDL-C level or HDL components could be worthy of further investigation. Metabolic disorders characterized by increases of proinflammatory cytokine IL-6 level in lung and circulating leptin could exacerbate pulmonary hypertension as a result of left heart disease (PH-LHD), and patients diagnosed with this type of PAH have more severe symptoms and worse prognosis relative to patients with LHD alone (4). Notably, in light of pulmonary vascular remodeling in such a novel preclinical model of PH-LHD relieved by metformin though improvement of metabolic states and decrease of inflammation, and positive effects of RVX-208 on the regulation of both inflammation and metabolism (3, 4), we thought that providing more insights about the efficacy of RVX-208 in PH-LHD might be more favorable to its clinical use. Epigenetic regulation plays a key role in the pathogenesis of PAH, such as drug/toxin susceptibility, female predominance, and quasimalignant lung vessel cell growth (5). In view of BET protein BRD4 (bromodomain-containing protein 4) as an epigenetic driver of inflammation and atherogenesis, the reduction of vascular inflammation *in vitro* and major adverse cardiac events in the patients with cardiovascular disease by the administration of RVX-208 has been considered to rely on a BET-dependent epigenetic mechanism (6). Therefore, we considered that clarifying additional epigenetic mechanisms underlying the therapeutic process of RVX-208 in PAH might be in favor of identifying putative biomarkers and risk or resilience factors for making new-type prevention and treatment to answer epigenetic-sensitive clinical challenges in PAH. ■

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Reply to Ning *et al.*

From the Authors:

We thank Ning and colleagues for their suggestions aimed at exploring whether RVX-208 therapy in pulmonary arterial hypertension (PAH) is associated with enhanced concentration of plasmatic high-density lipoprotein cholesterol (HDL-C), whether these anticipated changes contribute to the improvement of vascular remodeling and pulmonary hemodynamics seen in our models, whether the circulating HDL-C level can be used as a clinical biomarker in future PAH clinical studies, and whether our findings could be extrapolated to other forms of pulmonary hypertension (PH).

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As mentioned by Ning and colleagues, reduced HDL-C levels characterize patients with PAH and are associated with worse prognosis (1). Interestingly, RVX-208 (apabetalone) was originally developed as a lipid-modifying agent, inducing hepatic synthesis of apoA-I (apolipoprotein A-I) and enhancing the cholesterol efflux capacity of HDL. However, early studies evaluating the administration of apabetalone in patients with coronary artery disease (CAD) revealed modest elevation of apoA-I and HDL-C (2), suggesting that apabetalone may have actions beyond those on lipoproteins. As a result of their ability to bind acetylated histone tails, as well as to interact and modulate the activity of many regulators of transcription, members of the bromodomain and extra-terminal domain protein family such as BRD4 (bromodomain-containing protein 4) are implicated in many cellular processes and cell growth. As such, their inhibition is expected to exert pleiotropic actions, concomitantly affecting different aspects of PAH pathophysiology.

We consistently documented previously that BRD4 inhibition reversed the oncogenic NFAT, Bcl-2, and survivin upregulation, restoring the PAH–pulmonary artery smooth muscle cell proliferation/apoptosis imbalance and improving pulmonary hemodynamics in PH rat models (3). We also documented that BRD4 expression was increased in coronary arteries of patients with PAH, contributing to vascular remodeling and the development of concomitant CAD (4). Interestingly, BRD4 is also known to regulate RUNX2, which accounts for calcification lesions seen in PAH (5, 6). Of note, the effects of BRD4 inhibition on PAH and CAD were at least in part mediated through its effects on metabolism and inflammation (4, 7). As proposed by Ning and colleagues, whether these findings could be extrapolated to other types of PH characterized by inflammatory and metabolic disturbances such as group 2 PH occurring in the setting of a metabolic syndrome (8) certainly represents a research priority, given the significant unmet medical needs for these patients.

Obviously, the enhanced HDL-C levels after RVX-208 treatment may also have contributed by itself to the structural and hemodynamic improvements reported in our PAH models (4, 7). Consistent with the pleiotropic effects described here, however, the recent pooled analysis of clinical trial phase 2 studies in patients with CAD confirmed that apabetalone reduced the incidence of major adverse cardiovascular events, despite marginal effects on their lipid profile (2). Of interest, exploratory analyses suggested that this reduction in major adverse cardiovascular events was most predominantly observed in patients with low HDL-C, elevated inflammation levels, or diabetes at the baseline. As HDL-C positively correlates with systemic inflammatory markers (IL-1b, IL-6, MCP-1 [monocyte chemoattractant protein-1], and TNFα [tumor necrosis factor α]), apabetalone did not translate either to regression of coronary atherosclerosis volume in patients with CAD or to changes in blood glucose and had only a marginal benefit on inflammation levels (2). The exact mechanisms by which apabetalone prevented major adverse cardiovascular events remains elusive. Accordingly, in addition to accumulating mechanistic insights, whether baseline alterations in DNA repair pathways, procalcification processes, inflammation and metabolic defects, or changes upon treatment identify potential biomarkers predicting or paralleling response to BRD4 inhibition, allowing the molecular stratification of patients with PAH and precision medicine will be explored in our ongoing clinical study (APPRoAcH; clinical trial registered with www.clinicaltrials.gov [NCT 03655704]), evaluating apabetalone in PAH. ■

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Improving Lung Function in Severe Heterogenous Emphysema with the Spiration Valve System: Still a Great Need to "EMPROVE"

To the Editor:

We read with keen interest the results of a randomized controlled trial of the Spiration Valve System in patients with severe emphysema by Criner and colleagues (1). We congratulate the authors for presenting a well-designed study on an important clinical question. It has been previously reported that use of endobronchial valves in severe emphysema leads to improvement in FEV_1 compared with placebo, similar to the results found in the present study (2). However, some important points regarding the reported results need careful consideration and further discussion.

Although the authors report significant improvement in FEV_1 compared with baseline on 6-month follow-up in the valve group, the overall responder rate is only 37%; that is, only approximately one-third of all patients who received the valve actually demonstrated benefit in airflow. Similarly, although the patient-centered outcomes (i.e., dyspnea and quality of life) improved in the valve group, they did so in only 53% and 54% of subjects, respectively, at 6 months. We feel that this response rate is extremely low by any standard, especially considering the high cost and potential complications associated with valve placement. Therefore, it would be desirable to interpret these results in the proper perspective, based on cost benefit.

Considering the patient population in which endobronchial valve therapy is being considered (i.e., those with severe airflow limitation, limited exercise capacity, and receiving long-term oxygen therapy), it may be worthwhile to identify predictors of nonresponse in the endobronchial valve therapy group in an attempt to identify patients most likely to derive benefit from this intervention. This may have important implications for rationalizing clinical practice of emphysema management. ■

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Reply to Jain *et al.*

From the Authors:

We thank Dr. Jain and colleagues for their comments about our study. We wholeheartedly agree that refining the patient population most likely to benefit from this or any other therapy is the goal of personalized patient care. The cost of care, especially in the case of patients with emphysema, is also of prime importance. However, we would like to emphasize that despite the severity of the patient group studied in EMPROVE (patients with severe and irreversible airflow obstruction [FEV_1, 28–30% predicted], hyperinflation [residual volume, 207–213% predicted], and >60% emphysema severity in the targeted lobes), patients with valve treatment were sevenfold more likely to achieve >15% improvement in FEV_1 at 1 year compared with the control group receiving optimal medical therapy (1). In addition, as pointed out by Dr. Jain, more than half the subjects exceeded the minimally important changes in dyspnea and quality of life. This was balanced against the complication of pneumothorax, a treatable consequence of endobronchial valve treatment with total lobar occlusion in subjects with fissure integrity. We believe it is also important to consider the alternative therapies used to treat patients at this stage of their disease and their symptom

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