Boucly and colleagues (3), which investigated the impact of initial treatment strategy on the long-term prognosis of PAH by a comprehensive subgroup analysis and propensity score matching method and demonstrated tremendous survival benefits of initial triple combination therapy including parenteral prostacyclin for high-risk patients with PAH at the time of diagnosis. Excitingly, this is the first study showing a favorable profile of initial triple combination therapy with parenteral prostacyclin in intermediate-risk patients with PAH. However, the initial triple combination strategy is highly controversial among patients with intermediate- and high-risk PAH.

Three differential signaling pathways integrated in triple combination therapy, namely, the endothelin, nitric oxide, and prostacyclin pathways, may complement each other and produce superimposed or even synergistic effects (1). Gone are the days when patients with PAH had no available effective medicines, and with multiple accessible drugs advancing side by side and vying for the light, we have ushered in a new era of prosperity, so why not choose an optimized initial triple combination strategy? Moreover, a high proportion of triple combination therapies (including epoprostenol) enabled Japanese patients with idiopathic/heritable PAH to obtain a good long-term prognosis, with a 10-year survival rate of nearly 80%, suggesting more effectiveness of a relatively aggressive treatment strategy to rapidly reach low-risk status or hemodynamic normalization, especially for intermediate- and high-risk PAH (4). Additionally, although initial dual combination of PAH-targeted medications brought clinical benefits (5), the overall 10-year survival rate reported in the related study was only 43%, with 25% of patients with PAH receiving initial dual therapy escalated to triple combination therapy after a median follow up of 17 months (3), indicating the former strategy may result in disease progression and delayed optimal treatment.

Nonetheless, medication administration complexity, high drug expenses, targeted agent accessibility, and various adverse effects make initial triple combination strategy contentious and challenging. Unlike widely accepted oral medication, subcutaneous or intravenous administration of treprostinil requires complex up-titration to achieve an optimally tolerated dose. Regarding cost burden and drug accessibility, bosentan, macitentan, riociguat, and selexipag were already covered by Chinese national health insurance in 2019, but treprostinil has not been included. Furthermore, epoprostenol is not currently marketed in China, thus greatly limiting the therapeutic measures of critically ill patients. Last but not least, 19.0% of patients with PAH treated with selexipag, in the *post hoc* analysis of GRIPHON Study (evaluating a selexipag add-on to background dual combination therapy), prematurely discontinued their study regimen because of an adverse event, implying more side effects with more drugs (6).

Further prospective, multicenter, randomized controlled trials are needed to conclusively determine the optimal triple drug combination, and the role of initial triple therapy in other PAH subtypes, such as congenital heart disease or connective tissue disease–associated PAH, is also worth exploring. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Treatment of Pulmonary Hypertension: Is Triple Therapy Necessarily Better than Monotherapy?

To the Editor:

Recently, Boucly and colleagues (1) found that long-term survival was independently related to the initial treatment strategy in a large cohort of patients newly diagnosed with idiopathic, hereditary, or anorexin-induced pulmonary arterial hypertension (PAH). Initial triple therapy treatment, including parenteral prostacyclin, was associated with a better overall survival rate than monotherapy or dual therapy with or without parenteral prostacyclin. The authors further clarified the relationship between the initial treatment strategy and long-term survival rate in patients with PAH, providing a new

Supported by Science and Technology Special Fund of Guangdong Province in 2019 ("Major Projects + Task List") (Special Project for Major Science and Technology Innovation Platform and Project Introduction) No. 2019A201.

Originally Published in Press as DOI: 10.1164/rccm.202108-1965LE on October 14, 2021

basis for its treatment. However, this relationship has not been fully studied so far.

PAH is a life-threatening disease, and the median survival time of untreated adult patients is less than 3 years (2). It can be seen that the initial treatment strategy for PAH is vitally important. Studies have found that triple therapy for PAH reduced the risk and reversed right heart remodeling (3). In several randomized controlled trials and meta-analyses, it was proven that a combination of different approaches could improve hemodynamics, clinical function, and survival time (4). However, Stubbe and colleagues (5) showed that the 12-month survival rates of "atypical" and "typical" patients with PAH were similar. In the "atypical" PAH group, there was no difference in the 12-month survival rate between triple therapy patients and monotherapy patients. Therefore, there is still a little controversy about the prognosis of PAH between triple therapy and monotherapy.

In the study by Boucly and colleagues (1), the authors made comparisons after matching age, sex, and pulmonary vascular resistance to correct these confounding factors. However, compared with younger patients with PAH, those over 65 years of age had lower enthusiasm for being prescribed targeted PAH drugs, affecting the survival rate even after adjusting for age (5). In addition, other important prognostic variables such as echocardiography and cardiac magnetic resonance imaging were considered part of a comprehensive risk assessment strategy (6). However, the authors did not systematically collect or analyze them. Moreover, the authors did not compare the side effects caused by triple therapy and monotherapy. Although triple therapy improves the survival rate, the side effects of multiple drugs may further affect patients' quality of life, so it is also necessary to assess the long-term impact of the side effects. Furthermore, triple therapy is more expensive than monotherapy, which will invisibly eliminate some low-income patients and may cause the selected population to be less representative. The price will also affect the promotion of subsequent treatments. Therefore, it is necessary for us to conduct various subgroup analyses to further compare the benefits and risks of triple therapy. In addition, the authors' research is aimed at idiopathic PAH. However, there are many patients with secondary PAH in clinics, and whether the same results arise between triple therapy and monotherapy requires further verification. Finally, we suggest that the authors can further analyze the decision curve and clinical impact curve to evaluate the clinical efficacy of triple therapy and provide further proof. At present, there are few large-scale randomized controlled studies on triple therapy for PAH, and there is a lack of evidence in this regard. We look forward to conducting prospective multicenter randomized controlled studies to further evaluate the efficacy of initial triple therapy and monotherapy or double therapy. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

Acknowledgment: The authors thank Prof. Nanshan Zhong from the State Key Laboratory of Respiratory Disease for his constructive advice.

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