



## ARTICLE

Association Between Initial Treatment Strategy and Long-term Survival in Pulmonary Arterial Hypertension (PAH) <https://pubmed.ncbi.nlm.nih.gov/34185620/>

## CLINICAL QUESTION

How is long-term survival in patients with PAH affected by initial risk status and treatment strategy?

## SUMMARY

The 2015 ERS/ESC guidelines on PAH recommend initial risk stratification of newly diagnosed patients with PAH and tailoring therapy according to their risk profile. Combination therapy (including intravenous prostacyclins) is recommended for those with a high-risk profile. For patients with low and intermediate risk profile, either monotherapy or dual oral therapy is recommended. No study has evaluated the impact of initial treatment strategy (monotherapy versus dual-combination therapy versus triple-combination therapy) on long term survival of patients with PAH.

This study retrospectively analyzed patients with incident idiopathic, heritable, or anorexigen-induced PAH enrolled in the French PH Registry and the choice of initial therapy on long-term survival.

### **Subjects:**

Newly diagnosed idiopathic, heritable, and anorexigen-induced PAH patients enrolled in the French PAH Registry between January 2006 and December 2018 were included. Patients with other causes of PAH such as systemic sclerosis or portopulmonary hypertension were excluded. Only patients receiving therapy within 3 months of diagnosis were included and those on calcium channel blocker monotherapy were excluded. Patients were stratified according to initial treatment regimen; monotherapy, dual-combination therapy, or triple-combination therapy (including parenteral prostacyclin).

### **Methods:**

Survival was analyzed according to initial therapy in the overall population, as well as according to risk assessment at baseline, according to the abbreviated ESC/ERS risk stratification based on the number of low-risk criteria present (Functional class I-II, 6-minute walk distance >440m, right atrial pressure < 8 mmHg, and cardiac index >2.5L/m<sup>2</sup>). The effect of initial therapy was also analyzed in the subset of patients on parenteral therapy. Survival analysis was performed using the Kaplan Meier method and an intent-to-treat analysis.

Additional survival analysis was performed using propensity score matching on age, sex, and pulmonary vascular resistance.



## Results:

1611 patients were included. 984 patients (61%) were initially treated with monotherapy, 551 (34%) with dual-combination therapy, and 76 (5%) with triple-combination therapy.

Patients initiated on triple-combination therapy were younger with less comorbidities and more severe disease. 91% of patients on initial triple-combination therapy had zero or one low-risk criteria, as compared to 72% of those on dual oral therapy and 57% of those on monotherapy. After a median 5 months follow up, 78% of patients on triple-combination therapy achieved three or four low risk criteria, compared to 47% and 36% of those on dual-combination therapy or monotherapy, respectively.

The patients were followed for a median period of 32 months. Overall, triple-combination therapy was associated with a 91% survival at 5 years compared to 61% in the dual-combination or monotherapy groups. Triple-combination therapy was also associated with higher transplant-free survival (75% vs 56% and 58% at 5 years). When matching for age, sex, and PVR, overall survival benefit with triple therapy persisted.

In the 15% of patients with baseline high-risk status, survival was significantly higher in the initial triple-combination therapy group, while there was no difference in the monotherapy and dual-combination therapy groups. In patients with intermediate risk, initial triple therapy was also associated with a significant survival benefit, while dual-combination therapy was superior to oral monotherapy. In patients with low-risk status, initial monotherapy or dual-combination therapy were associated with similar survival rates.

In the subgroup that received initial parenteral therapy (9%), initial triple-combination therapy was associated with a significant survival benefit as well.

## GROUP OPINION

In this large retrospective cohort study, initial triple-combination therapy was associated with an impressive overall survival benefit compared to dual-combination or monotherapy. This survival benefit was observed despite the patients on triple therapy having more severe disease. This study currently adds to the argument for an aggressive treatment strategy in high risk and intermediate risk patients. Furthermore, the survival benefit observed does not appear to be due to prostacyclin therapy alone, but rather the combination of PAH drugs, suggesting synergistic effects. This study supports the use of risk assessment in patients with PAH and a treatment strategy guided by the patient's risk status, with triple-combination strategy including a parenteral prostacyclin, being likely beneficial in patients with high and intermediate risk. Note that they did not examine oral prostacyclin pathway therapies (oral treprostinil or selexipag) in this study. Furthermore, the initial choice of combination therapy may have been influenced by clinical parameters not assessed by ERS/ESC risk-assessment tool, such as systemic hypotension,



that would have limited the number of agents and adversely affected outcome. Despite the limitation of this retrospective study, the results are noteworthy and warrant discussion of our approach to management of the PAH patient.

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