



Pulmonary Arterial Hypertension: Upfront Triple Therapy and the Shift Away from Sequential Escalation

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Introduction

For most of its modern treatment era, pulmonary arterial hypertension was managed the way much of chronic cardiovascular disease still is: start one drug, and add a second or third only once the first has visibly failed. That sequential-escalation default has been challenged directly by randomized trials testing upfront combination therapy from the moment of diagnosis, first as two drugs together, and more recently as three.

This review sets out what upfront double therapy has established about clinical outcomes, what a subsequent trial of upfront triple therapy did and did not add, and how current guidelines have translated this evidence into risk-stratified treatment recommendations at diagnosis.

Material and Methods

This is a narrative review drawing on the AMBITION randomized trial and its subsequent hospitalization sub-analysis, the TRITON randomized trial, and the 2022 ESC/ERS pulmonary hypertension guidelines, identified through the sources cited above and citation tracking between them, without a pre-registered protocol or systematic search string. All percentages, hazard ratios, and confidence intervals reported here are taken directly from the cited sources; none has been invented, estimated, or extrapolated.

Results

AMBITION: upfront double therapy halved the risk of clinical failure

AMBITION randomized 500 treatment-naïve patients with PAH to initial combination therapy with ambrisentan plus tadalafil (n=253) or to ambrisentan (n=126) or tadalafil (n=121) monotherapy [1]. The primary composite clinical-failure endpoint -- death, hospitalization for worsening PAH, disease progression, or unsatisfactory long-term clinical response -- occurred in 18% of the combination group versus 31% of pooled monotherapy (HR 0.50, 95% CI 0.35-0.72, P<0.001) [1]. Figure 1 sets this primary outcome out directly.

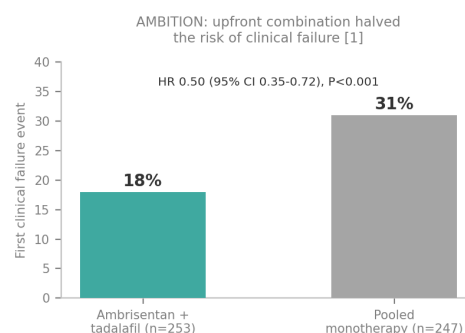


Figure 1: Primary composite clinical-failure endpoint, initial ambrisentan plus tadalafil versus pooled monotherapy, AMBITION trial [1].

Functional capacity and biomarkers improved further with combination therapy

Six-minute walk distance improved by a median of 48.98 m with combination therapy versus 23.80 m with pooled monotherapy from baseline to week 24 ($P<0.001$) [1]. NT-proBNP fell by a geometric mean of 67.2% with combination therapy versus 50.4% with pooled monotherapy over the same period ($P<0.001$) [1]. Figure 2 sets both secondary outcomes out together.

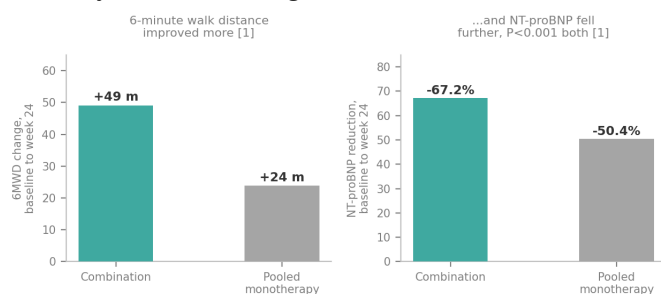


Figure 2: 6-minute walk distance change and NT-proBNP percent reduction, baseline to week 24, initial combination versus pooled monotherapy, AMBITION trial [1].

Fewer hospitalizations accounted for much of the clinical-failure benefit

Hospitalization for worsening PAH occurred in 4% of the combination group versus 12% of pooled monotherapy [1]. Figure 3 sets this out: among the four components of the composite clinical-failure endpoint, hospitalization showed the largest absolute difference between strategies, suggesting that upfront combination therapy's benefit is concentrated substantially in preventing acute clinical deterioration severe enough to require admission.

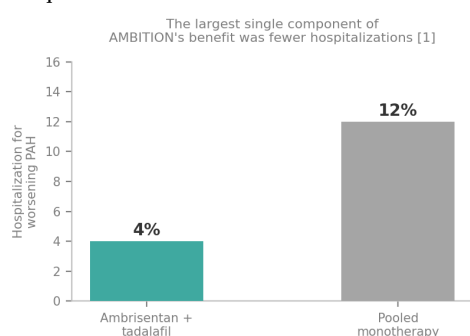


Figure 3: Hospitalization for worsening PAH, initial combination versus pooled monotherapy, AMBITION trial [1].

TRITON: adding a third upfront drug did not improve the primary endpoint

TRITON randomized 247 patients with newly diagnosed PAH to initial triple oral therapy (macitentan, tadalafil, and selexipag; $n=123$) or initial double therapy (macitentan and tadalafil plus placebo; $n=124$) [2]. The primary endpoint, pulmonary vascular resistance reduction from baseline to week 26, showed no significant difference between groups (-54% triple vs -52% double, treatment-effect ratio 0.96, 95% CI 0.86-1.07, $P=0.42$) [2]. Figure 4 sets this null primary result out directly.

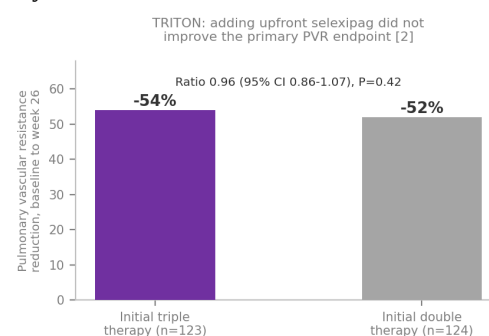


Figure 4: Pulmonary vascular resistance reduction, baseline to week 26, initial triple versus initial double oral therapy, TRITON trial [2].

A numerically lower rate of disease progression and hospitalization, not independently significant

Over a median follow-up of 1.5 years, a first disease-progression event occurred in 13.0% of the triple-therapy group (16 of 123 patients) versus 21.8% of the double-therapy group (27 of 124 patients), HR 0.59 (95% CI 0.32-1.09) [2]. Hospitalization occurred in 8% of the triple-therapy group versus 15% of the double-therapy group, and there were no deaths in the triple-therapy group versus four in the double-therapy group [2]. Figure 5 sets both secondary comparisons out together; because TRITON was not powered for these endpoints and its confidence interval for disease progression crosses 1.0, neither difference can be read as statistically confirmed.

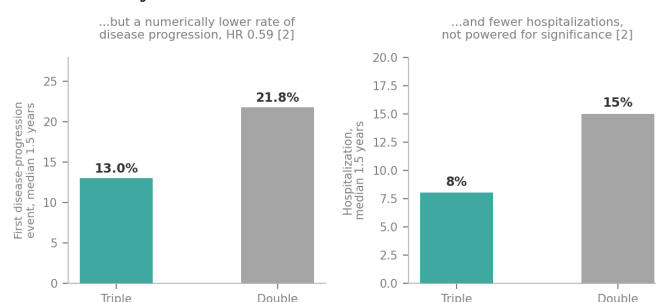


Figure 5: Disease-progression events and hospitalization, median 1.5 years follow-up, initial triple versus initial double oral therapy, TRITON trial [2].

Guidelines now stratify upfront combination therapy by risk at diagnosis

The 2022 ESC/ERS pulmonary hypertension guidelines formalize this evidence into a risk-stratified initial-therapy recommendation: for newly diagnosed patients without cardiopulmonary comorbidities at low or intermediate-low risk, initial combination therapy with an endothelin receptor antagonist (ERA) and a phosphodiesterase type 5 inhibitor (PDE5i) is recommended; for those at high risk, initial combination therapy with an ERA, a PDE5i, and a parenteral prostacyclin analogue should be considered [3]. Figure 6 sets this risk-stratified schema out schematically. Sequential escalation, once the default starting point for essentially all newly diagnosed patients, is now reserved for reassessment during follow-up rather than for the initial treatment decision itself.

2022 ESC/ERS guidelines: initial combination therapy is now risk-stratified at diagnosis, not reserved for treatment failure [3]

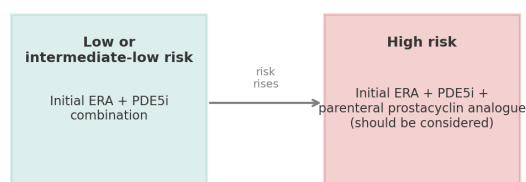


Figure 6: Risk-stratified initial combination therapy at diagnosis, 2022 ESC/ERS pulmonary hypertension guidelines [3].

Discussion

These three sources together describe a specific and bounded shift, not a uniform move toward maximal upfront therapy for everyone. Upfront double therapy's clinical-outcome benefit is now well established by a large randomized trial with a clinically meaningful primary endpoint, and that evidence is what current guidelines build their low-to-intermediate-risk recommendation on. Upfront triple therapy's evidence base is thinner: its one dedicated randomized trial missed its primary hemodynamic endpoint, and its more clinically relevant secondary findings, while directionally favorable, were not statistically confirmed in a trial sized for a different question. The guideline recommendation for high-risk patients to have a prostacyclin analogue considered from diagnosis rests more on the biological rationale for aggressive early treatment in a high-mortality subgroup than on a TRITON-sized demonstration of superiority.

For a clinician managing a newly diagnosed patient, the evidence supports upfront ERA plus PDE5i combination therapy for low-to-intermediate-risk disease with real confidence, while treating the addition of a third upfront agent in high-risk disease as a guideline-endorsed, biologically motivated recommendation rather than one confirmed by a definitive clinical-outcome trial.

Study limitations

This is a narrative review, not a systematic review with a pre-registered protocol, and it draws on two randomized trials of different scale and design: AMBITION compared combination therapy against monotherapy with a clinically meaningful composite endpoint in 500 patients, while TRITON compared triple against double therapy with a surrogate hemodynamic primary endpoint in a substantially smaller population of 247 patients, so the two trials are not directly comparable in what they can demonstrate. TRITON's secondary findings on disease progression and hospitalization, while numerically favorable to triple therapy, were not the trial's statistically powered primary comparison and should be interpreted with the caution appropriate to underpowered secondary endpoints. Neither trial was designed to isolate which single added drug class drives its observed benefit, so this review cannot say whether an ERA, a PDE5i, or a prostacyclin pathway agent contributes most to the outcomes described.

Conclusion

Upfront double combination therapy with an ERA and a PDE5i has a well-established clinical-outcome benefit in newly diagnosed pulmonary arterial hypertension, reducing clinical failure by half and hospitalization by two-thirds compared with monotherapy. Upfront triple therapy's added value beyond double therapy remains genuinely unresolved: its dedicated randomized trial did not meet its primary hemodynamic endpoint, even as its secondary clinical findings pointed in a favorable, if statistically unconfirmed, direction. Current guidelines now organize this evidence into a risk-stratified recommendation at diagnosis, reserving the strongest upfront combinations for the highest-risk patients rather than waiting for treatment failure to prompt escalation.

Neither trial reviewed here enrolled substantial numbers of patients with connective-tissue-disease-associated PAH or other non-idiopathic etiologies known to respond differently to therapy, so this review's conclusions apply most directly to the idiopathic and heritable PAH populations that predominated in both trials, and should not be assumed to generalize unchanged to etiologies with a different underlying vasculopathy.

A further practical implication concerns how risk is reassessed after initial therapy is started. The guideline framework described here applies chiefly to the moment of diagnosis; what happens when a patient started on upfront double therapy is later found to be at intermediate-high or high risk on follow-up assessment is a distinct clinical question, governed by the guidelines' separate follow-up risk-reassessment recommendations rather than by the initial-therapy evidence reviewed here, and a dedicated trial directly comparing early intensification strategies at that later decision point would meaningfully extend what AMBITION

and TRITON, both trials of initial therapy, can currently tell us.

Cost and access considerations also shape how readily this evidence translates into practice outside the trial setting. Parenteral prostacyclin analogues require infusion pumps, central venous or subcutaneous access, and a level of patient and caregiver training that is not equally available across health systems, so the guidelines' high-risk recommendation, however well supported in principle, may be adopted unevenly wherever that infrastructure is scarce. Oral triple therapy of the kind tested in TRITON avoids that specific barrier, which is part of why its evidence base, even though it missed its primary endpoint, continues to attract clinical interest as a potentially more deliverable alternative to upfront parenteral therapy in high-risk patients who cannot readily access infusion-based care.

Trial	N	Comparison	Primary outcome	Result
AMBITION [1]	500	Combo vs pooled mono	Composite clinical failure	HR 0.50 (0.35-0.72)
TRITON [2]	247	Triple vs double	PVR reduction, week 26	-54% vs -52%, P=0.42

Table 1: Design and primary-outcome result of the two randomized upfront-combination-therapy trials reviewed here [1,2].

It is worth restating AMBITION's secondary findings alongside its primary result, since they describe a consistent pattern rather than an isolated endpoint: 6-minute walk distance improved more with combination therapy (48.98 m vs 23.80 m), NT-proBNP fell further (67.2% vs 50.4%), and hospitalization for worsening PAH was roughly a third as frequent (4% vs 12%) [1]. Every prespecified measure in AMBITION points the same direction, which is part of why its result has been adopted into guidelines with more confidence than TRITON's numerically favorable but statistically unconfirmed secondary findings have been.

TRITON's mortality signal, though based on very small numbers, deserves a similarly careful restatement rather than being folded silently into the broader 'not statistically confirmed' verdict on its secondary endpoints: zero deaths occurred in the triple-therapy group over a median 1.5 years of follow-up, versus four deaths in the double-therapy group [2]. Four events in 124 patients is far too few to support any claim about a mortality benefit, and TRITON was not designed or powered to make one, but the direction of every secondary endpoint the trial reported -- disease progression, hospitalization, and death alike -- was consistent, even where individual confidence intervals crossed the null.

The 2022 ESC/ERS guidelines' own risk-stratification scheme, referenced above, is itself built from a broader evidence base than AMBITION and TRITON alone, incorporating validated risk calculators that combine

functional class, 6-minute walk distance, NT-proBNP, and hemodynamic parameters into a single risk category at diagnosis [3]. That risk category, not the trial evidence for double or triple therapy considered in isolation, is what ultimately determines which upfront regimen a given newly diagnosed patient is recommended to start, which is why this review's conclusions about AMBITION and TRITON should be read as informing one input to that broader risk-stratified decision rather than as a standalone treatment algorithm.

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