Gaps and Controversies of New Treatment Recommendations in Recent Pulmonary Hypertension Guidelines: What We Know and What We Don't

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Pulmonary arterial hypertension (PAH) is a rare, severe disease of the small pulmonary arteries that is characterized by increased pulmonary vascular resistance and ultimately progression to right heart failure.[1] Broadly categorized as World Health Organization (WHO) Group 1 PAH, it encompasses a heterogeneous group of underlying disorders.[2-4] Despite the development of new treatment options and strategies over the past 2 decades, survival rates in newly diagnosed patients at 5 years are only 61.2%, and are even poorer in patients with advanced disease.[5]

New European Society of Cardiology (ESC)/European Respiratory Society (ERS) pulmonary hypertension guidelines were released in 2015, with redesigned treatment algorithms aimed at addressing the recent advances in PAH medications, treatment initiation strategies, and treatment goals.[3] Though much progress has been made, many areas of uncertainty remain, and some aspects of the 2015 ESC/ERS recommendations are still controversial. Herein, we will discuss some of the gaps and controversies within the recommendations for treatment-naïve WHO Group 1 PAH patients.

MONOTHERAPY VS COMBINATION THERAPY

The 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) pulmonary arterial hypertension (PAH) treatment algorithm recommends: in patients who are low to intermediate risk, are World Health Organization (WHO) functional class (FC) II-III, are treatment-naïve, and are either not candidates for or are non-responders to acute vasoreactivity, oral monotherapy or oral combination therapy should be the initial treatment.[3] The data underlying this recommendation, however, do not demonstrate the same therapeutic equivalency.

Pulmonary arterial hypertension is a multifactorial disease with complex pathophysiology. Our current therapies target 3 distinct therapeutic pathways: nitric oxide-cyclic guanosine monophosphate (NO-cGMP) enhancement, prostacyclin pathway agonism, and endothelin pathway antagonism.[1] Despite the therapeutic effectiveness of each drug class, no single class or pathophysiological target is uniformly effective in treating all patients, lending a supportive rationale to the argument for combination therapy as is typically utilized in other chronic medical conditions such as heart failure, cancer, or HIV.

Previous short-term trials examining combination therapy failed to consistently show benefits, possibly confounded by inherent limitations in 6-minute walk distance (6MWD) as a primary endpoint and surrogate of outcomes in these populations.[6-17] Indeed, only with the recent onset of event-driven trials has combination therapy demonstrated consistent improvement in long-term outcomes.[19-21]

The AMBITION trial was a double-blind, randomized, controlled trial (RCT) that evaluated up-front combination therapy with ambrisentan and tadalafil, vs monotherapy with each agent alone in treatment-naïve WHO FC II-III PAH patients.[19] The primary endpoint was a composite of parameters of clinical failure; the combination of ambrisentan and tadalafil demonstrated significantly decreased rates of clinical failure events compared to monotherapy with either agent alone (hazard ratio [HR] for the combination group vs the pooled monotherapy group of 0.5 [95% confidence interval (CI), 0.35 to 0.72; $P<0.001$) (Figure 1).[19] This decreased rate of clinical failure events in the combination group was also observed across WHO functional class, for both FC II and FC III patients.[19] Statistically significant improvements from baseline brain natriuretic peptide (NT-proBNP) and 6MWD, respectively, were also noted at Week 24 in the combination therapy group over both the pooled and individual monotherapy groups. These findings emphasize the benefit of early initiation of combination therapy in any patient who meets the criteria that were used for entry into AMBITION.[19]

Additionally, a recently published post hoc subgroup analysis of the AMBITION trial confirmed the benefit of up-front combination ambrisentan and tadalafil in the connective tissue disease-associated PAH (CTD-PAH) cohort, inclusive of all CTD-PAH patients

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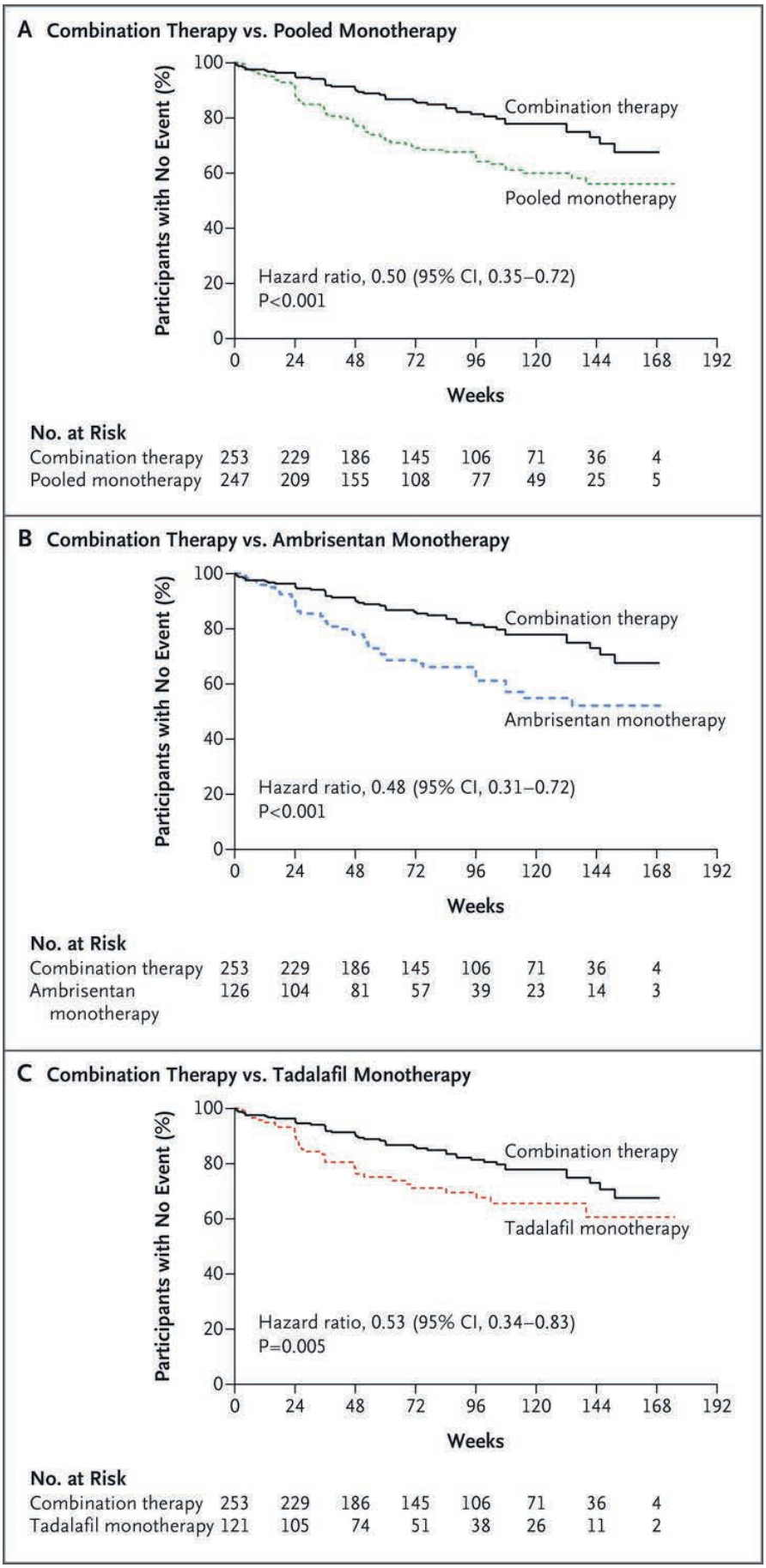

Figure 1: Kaplan–Meier curves for the probability of a first adjudicated primary endpoint event. The primary endpoint in a time-to-event analysis was the first event of clinical failure, which was a composite of death, hospitalization for worsening PAH, disease progression, or unsatisfactory long-term clinical response. The analyses were performed in the primary-analysis set, which comprised all participants who underwent randomization, received a study drug, and met amended entry criteria (which excluded participants with 3 or more risk factors for left ventricular diastolic dysfunction and set more stringent hemodynamic requirements than those in the original eligibility criteria). From Galiè N, Barberà JA, Frost AE, et al; AMBITION Investigators. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. *N Engl J Med*. 2015;373(9):834-844. Copyright © 2015 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

as well as the more specific subset of systemic sclerosis-associated PAH (SSc-PAH), over pooled or individual monotherapy (HR 0.43 [95% CI 0.24 to 0.77] and 0.44 [0.22 to 0.89], respectively).[22] These findings are especially noteworthy, given the poor prognosis of this latter subgroup compared to their idiopathic PAH (IPAH) counterparts, especially with monotherapy.[22] Furthermore, in an open-label trial of ambrisentan and tadalafil as up-front combination therapy in treatment-naïve WHO FC II-III patients with SSc-PAH, Hassoun et al observed decreased right ventricular (RV) mass (14% decrease, $P<0.05$) and decreased pulmonary vascular resistance (PVR) (55% decrease, $P<0.010$) at 36 weeks, again suggesting significant treatment response from combination therapy.[23]

It remains unclear if the benefit of up-front combination therapy seen in AMBITION is a drug effect, specific to ambrisentan and tadalafil in combination, a class effect, or whether these results are also generalizable to additional therapeutic combinations, because other RCTs comparing up-front combination therapy to monotherapy alone are lacking. Notably, COMPASS-2, a double-blind phase 4 RCT with a composite primary endpoint of morbidity/mortality in which patients on background stable-dose sildenafil were randomized to receive bosentan or placebo, observed no difference in the rate of clinical failure events.[18] Given the results of AMBITION, it is

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not clear why this study did not meet its primary endpoint; the authors cite limitations in study design and missing data from the primary endpoint as possible contributions.[18] However, it is also possible that this combination is not effective, possibly because of known drug-drug interactions between the 2 agents.[24]

The decrease in clinical failure events was also noted in 2 longer-term event-driven trials, SERAPHIN and GRIPHON, investigating the effect of macitentan and selexipag, respectively, in patients with PAH where the majority were receiving stable background therapy.[20-21] These will be discussed further below.

Given these observations and the premise of multifactorial PAH pathobiology as a rationale for a multitargeted combination therapy, one could surmise the possibility of increasing benefit with the addition of each distinct therapeutic intervention. This inevitably leads to the question: is *more* better? Retrospective data of up-front triple combination therapy with epoprostenol, bosentan, and sildenafil in newly diagnosed New York Heart Association (NYHA) FC III-IV PAH patients noted statistically significant improvement in NYHA FC, 6MWD, and cardiopulmonary hemodynamics at 4 months.[25] Additionally, predicted survival was 100% at 1, 2, and 3 years in the combination therapy cohort as predicted from the French registry risk equation.[25] Though these data are uncontrolled, the patients treated in this manner were very advanced with evidence of right heart failure; the demonstrable benefit of this study plus the beneficial effect of selexipag in patients on combination background therapy provides provocative preliminary evidence for long-term triple combination therapy.[25] In fact, there are currently 2 different phase 3 double-blinded RTCs underway that are evaluating dual vs triple up-front oral combination therapy in treatment-naïve PAH patients.[26-27]

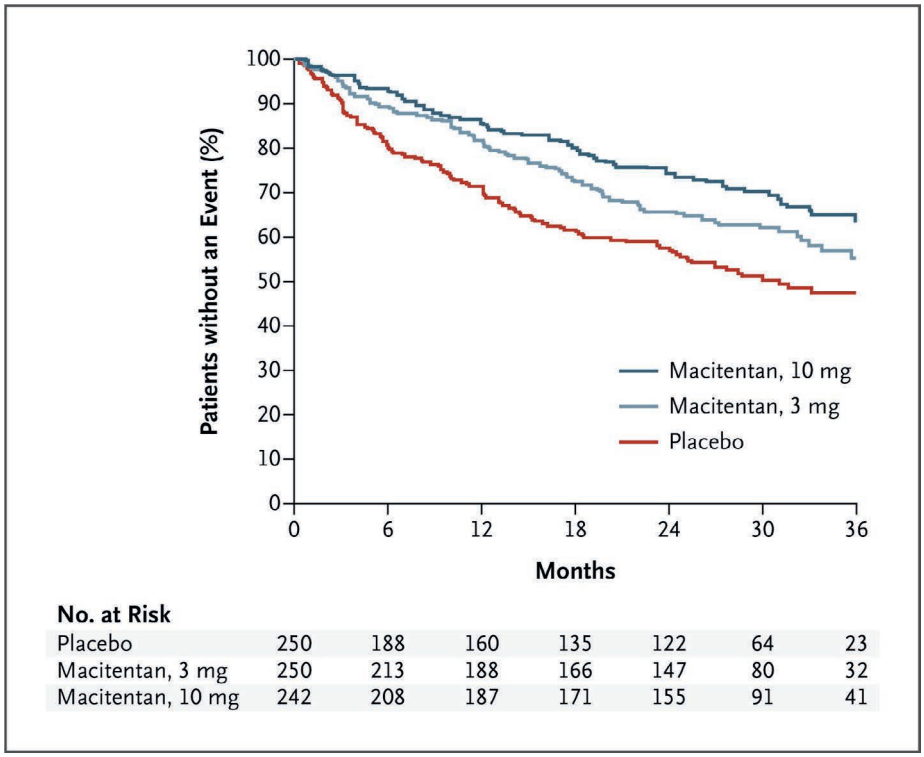
Given the preponderance of evidence demonstrating the benefits of combination therapy including decreased progression of disease, the equivalency of initial monotherapy vs combination therapy in the ESC/ERS PAH treatment algorithm is perplexing. While more data are needed to help ascertain whether these benefits are transferable for various other drug combinations as well as for increasing therapeutic targets, the magnitude of the benefit thus far demonstrated is indisputable and should prompt providers to preferentially initiate combination therapy in treatment-naïve PAH patients, if possible.

UP-FRONT VS RAPID SEQUENTIAL THERAPY

Combination therapy can be initiated "up front" (ie, all at once or initial combination therapy) or "sequentially" (ie, started in succession or one after the other over a short time frame). Regardless of the method used, the timing of each therapeutic addition for the treatment-naïve PAH patient remains an area with little definitive guiding data.

Up-front treatment with combination therapy has been evaluated in 2 RCTs.[14,19] BREATHE-2 was a short-term phase 3 study in which epoprostenol was combined with bosentan or placebo in treatment-naïve FC III or IV PAH.[14] Although the results trended toward a decrease in the primary endpoint, total pulmonary resistance (TPR), they did not reach statistical significance (P=0.08).[14] AMBITION has been discussed extensively above and demonstrated a 50% reduction in clinical failure events with combination ambrisentan and tadalafil compared to pooled or individual monotherapy.[19]

Sequential combination therapy has been evaluated more extensively in RCTs than up-front therapy. The majority of these studies were short-term trials, utilized 6MWD as the primary endpoint, and yielded mixed results.[6-13,15-17] In contrast, 3 recent larger, long-term, event-driven trials have yielded more definitive results.[18,20-21]



No. at Risk							
Placebo	250	188	160	135	122	64	23
Macitentan, 3 mg	250	213	188	166	147	80	32
Macitentan, 10 mg	242	208	187	171	155	91	41

Figure 2: Effect of macitentan on the composite primary endpoint of a first event related to PAH or death from any cause. Kaplan–Meier estimates for the first event related to PAH (worsening of PAH, initiation of treatment with IV or subcutaneous prostanoids, lung transplantation, or atrial septostomy) or death from any cause show a significant treatment effect in favor of macitentan at a once-daily dose of 3 mg vs placebo (HR, 0.70; 97.5% CI, 0.52 to 0.96; P=0.01 by the log-rank test) and macitentan at a once-daily dose of 10 mg vs placebo (HR, 0.55; 97.5% CI, 0.39 to 0.76; P<0.001 by the log-rank test). The intention-to-treat analysis took into account all available data, whereas the Kaplan–Meier curve is truncated at 36 months. From Pulido T, Adzerikho I, Channick RN, et al; SERAPHIN Investigators. Macitentan and morbidity and mortality in pulmonary arterial hypertension. *N Engl J Med*. 2013;369(9):809-818. Copyright © 2013 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

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SERAPHIN was a double-blind phase 3 RCT of macitentan 3 mg or 10 mg compared to placebo in WHO FC II-III PAH patients with a composite endpoint of clinical failure events.[20] In this study, macitentan 10 mg demonstrated a 45% reduction ($P<0.001$) in clinical failure events compared to placebo (Figure 2).[20] Moreover, nearly two-thirds of the study population were receiving background PAH-specific therapy, 96% of which were phosphodiesterase-5 inhibitors (PDE-5i).[20] In this subgroup, the risk of the composite primary endpoint was reduced by 38% ($P=0.009$) compared to placebo.[20]

GRIPHON was a double-blind phase 3 RCT of selexipag vs placebo in WHO FC II-III PAH patients with a composite primary endpoint of clinical failure events as well.[21] In the overall study population, there was a 40% reduction in the primary endpoint compared to placebo ($P<0.001$) (Figure 3).[21] Of note, at baseline, 47% of the study population were receiving background PAH-specific monotherapy (15% with an endothelin receptor antagonist [ERA], 32% with a PDE-5i) and another 33% were receiving dual therapy (combination of an ERA and PDE-5i).[21] The reduction in the risk of morbidity/mortality in these prespecified subgroups was consistent with the primary study findings.[21] These results support the notion of sequential dual and triple combination therapy as a central treatment strategy in PAH with an ERA, PDE-5i, and/or an oral IP prostacyclin receptor agonist.

While the results of these 3 large, event-driven trials are impressive, they still offer little guidance when selecting a combination treatment strategy, both in terms of timing of drug initiation and drug selection. There are, notably, no head-to-head trials comparing an upfront treatment strategy to a rapid sequential strategy, and thus it remains to be seen if one strategy is superior to the other. Indeed, all of the sequential therapy trials are confounded by the duration of the PAH-specific background therapy prior to trial onset and its impact on RV remodeling and disease progression. More study on the timing of sequential therapy is warranted in order to better understand these issues.

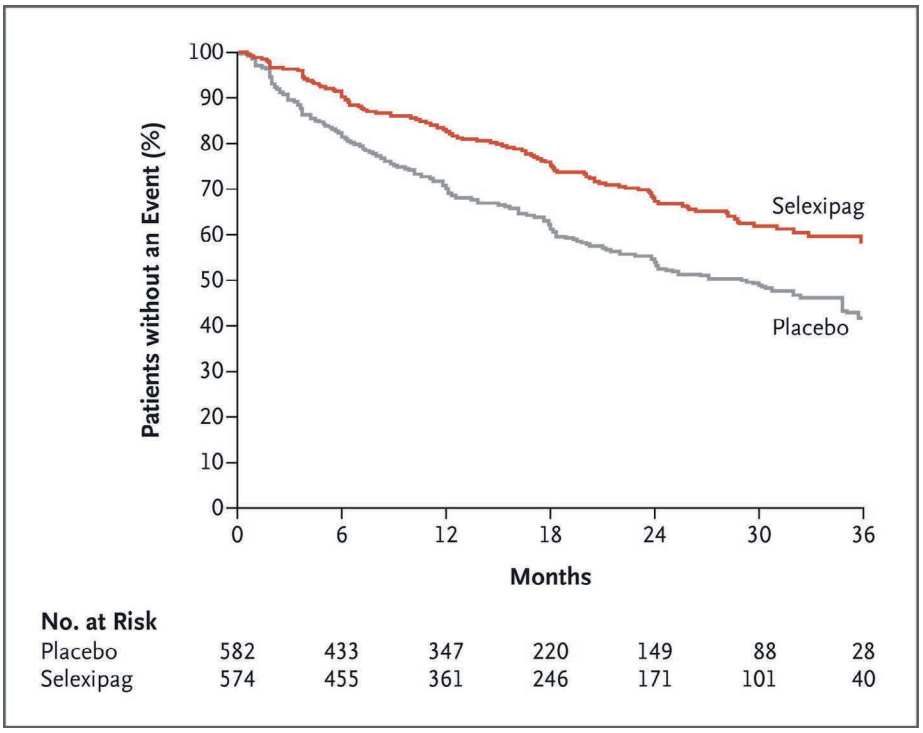

Figure 3: Primary composite endpoint. Shown are Kaplan–Meier curves for the primary composite endpoint of death (from any cause) or a complication related to PAH (disease progression or worsening of PAH that resulted in hospitalization, initiation of parenteral prostanoid therapy or long-term oxygen therapy, or the need for lung transplantation or balloon atrial septostomy) up to the end of the treatment period (defined for each patient as 7 days after the date of the last intake of selexipag or placebo) in the selexipag and placebo groups. A significant treatment effect in favor of selexipag vs placebo was observed (HR, 0.60; 99% CI, 0.46 to 0.78; $P<0.001$ with the use of a one-sided log-rank test). The analysis took into account all available data, whereas the Kaplan–Meier curve is truncated at 36 months. From Sitbon O, Channick R, Chin KM, et al; GRIPHON Investigators. Selexipag for the treatment of pulmonary arterial hypertension. *N Engl J Med*. 2015;373(26):2522-2533. Copyright © 2015 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

EQUIVALENCY OF DRUGS

Though the number of PAH-specific therapies has increased over the past 2 decades, there are no data directly comparing individual drugs or drug classes, even among subsets of Group 1 PAH. For drug selection within monotherapeutic regimens especially, where the choices between individual drugs or classes could have the greatest impact on patient outcome and response, the lack of data regarding therapeutic equivalency is problematic.

Intravenous (IV) prostacyclin analogues are recommended as first-line therapy for high-risk, treatment-naïve PAH patients.[3] Epoprostenol, an IV prostacyclin, is the most widely studied pulmonary vasodilator and is indicated for severe, decompensated PAH with a class I recommendation.[3] It has been shown to improve survival, hemodynamics, and 6MWD in PAH.[28] Treprostinil, an IV prostacyclin analogue, is also indicated in this patient population, though with less rigor as a class IIb recommendation.[3] There are no trials directly comparing the therapeutic equivalency of epoprostenol to IV treprostinil, although a small case series reported an inadequate clinical response in 5 patients with severe, decompensated PAH despite high-dose IV treprostinil.[29] These patients were transitioned to epoprostenol and all manifested a robust hemodynamic and functional response.[29] This suggests that there may be differential responses among some individuals to IV prostanoids, possibly secondary to variability of receptor targeting between the drugs.[29]

Among the other classes, there are observational, retrospective data in ERAs suggesting differential responses to therapy between different races and sexes.[30] Further study would be needed to confirm these findings.

With regard to combination therapies, the lack of data regarding the therapeutic

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equivalency of different combination partners has already been discussed. It is important to note that simply because a certain combination of drugs has demonstrated efficacy in a high-quality study, does not imply that other combinations from within those same classes will be equally as efficacious. To that point, the results from COMPASS-2 illustrate the importance of rigorous evaluation of the various permutations of combination partners available prior to declaring any particular combination effective.

Moreover, in the era of personalized medicine, the answers to these questions have become even more pressing as therapeutic equivalency may vary by subgroup and from person to person. Consideration of this in the design of future RCTs will be paramount, but very difficult to accomplish.

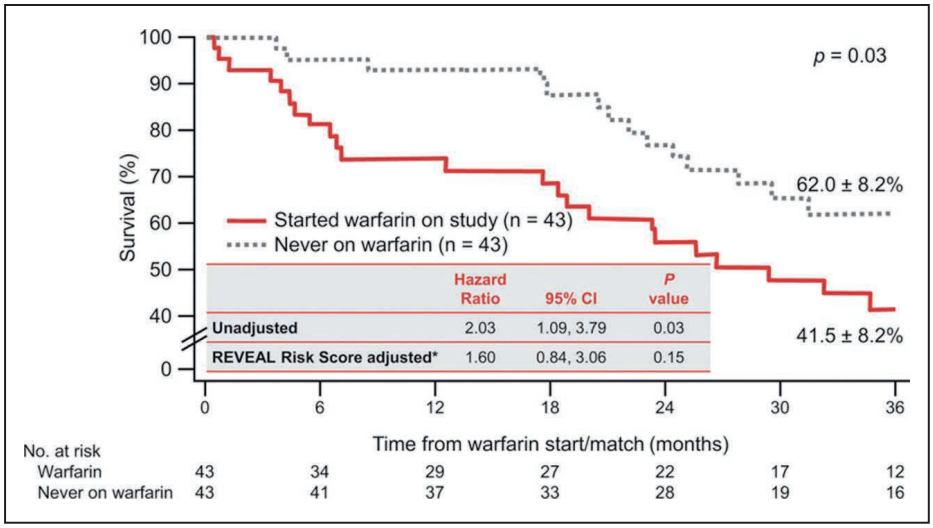

Figure 4: Kaplan-Meier estimates of survival at 36 months for SSc-PAH patients. CI indicates confidence interval; and SSc-PAH, pulmonary arterial hypertension associated with systemic sclerosis. *IPAH risk score at quarterly update corresponding to warfarin start. Reproduced with permission from Preston RJ, Roberts KE, Miller DP, et al. Effect of warfarin treatment on survival of patients with pulmonary arterial hypertension (PAH) in the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL). *Am J Respir Crit Care Med*. 2014;189:A2464.

WHAT DRUGS AND IN WHAT ORDER?

In treatment-naïve Group 1 PAH, the questions remain: what are the optimal therapeutic agents, and in what order should they be initiated? Initial combination therapy is now central to the treatment algorithm, and should be started in all patients who do not have contraindications and/or who are able to tolerate it. As previously stated, there are no data to help differentiate whether an up-front or a rapid sequential combination therapy strategy is superior. Sequential administration of combination partners does allow drug titration and evaluation of side effects more readily than up-front combination therapy; this should always remain a consideration. If pursuing a sequential route, initiating the second agent immediately upon completion of titration and evaluation of tolerance for the first agent (rapid sequential therapy; 3 months or less) may help to maximize benefits and minimize drug intolerance.

In selecting combination partners, there are unequivocal data to support the safety and efficacy of macitentan added to background PDE-5i (SERAPHIN), selexipag added to background PDE-5i and/or ERA (GRIPHON), and up-front combination ambrisentan + tadalafil (AMBITION).[19-21] Given the results of COMPASS-2, the specific combination of bosentan + sildenafil should be avoided pending results of further trials.[18] Other combinations within these drug classes have not been evaluated prospectively and may not demonstrate therapeutic equivalency.

ANTICOAGULATION

The 2015 ESC/ERS guidelines for pulmonary hypertension recommend that long-term anticoagulation be considered in IPAH, hereditary PAH (HPAH), and PAH due to the use of anorexigens with a class IIb recommendation.[3] Prior to the onset of the modern treatment era, several small observational studies supported a survival benefit in IPAH with anticoagulation.[31-33] A subsequent systematic review noted a total of 7 observational studies involving nearly 500 patients evaluating the effectiveness of warfarin in PAH, with 5 of those showing benefit.[34]

More recently, the COMPERA registry from the EU found a survival benefit that persisted up to 3 years in patients with IPAH who were treated with anticoagulation (HR 0.79; 95% CI 0.66-0.94); this survival benefit was not found in other subsets of PAH.[35] Notably, a post hoc analysis of the SSc-PAH subset showed a trend toward worse survival in those on anticoagulation, but this did not reach statistical significance (P=0.08).[35] In contrast, the REVEAL registry found no survival benefit with warfarin treatment in 187 IPAH patients with warfarin-naïve matched controls.[36] More importantly, however, the authors found that SSc-PAH treated with warfarin within the year prior or any time post-baseline had an increase in mortality ([HR 1.57, P=0.031] and [HR 1.49, P=0.046], respectively) (Figure 4).[36]

While the risk of thrombosis and thromboembolism in situ in this population is significant given an already compromised right ventricle,[31] the data are conflicting and do not conclusively settle the debate on anticoagulation. Though the registry trials offer the largest sample sizes and most robust data to date, more study is needed to determine the true risk/benefit profile of anticoagulation with warfarin in IPAH. Caution should be exercised with the use of warfarin anticoagulation in SSc-PAH, and it should be avoided unless a stronger indication is present (eg, pulmonary embolus).

Warfarin continues to be recommended in those patients receiving parenteral prostacyclins via tunneled lines, although there are no supportive data.[3] Likewise there are no data on the use of direct oral anticoagulants in this population, and they should be avoided pending results of future studies.

CONCLUSION

The field of pulmonary hypertension has experienced a rapid acceleration of

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knowledge in the past 2 decades with the development of new drug therapies and more robust RCT data. Early combination therapy has now become a central tenant of PAH treatment, with several clearly efficacious treatment regimens already identified. Though more study is warranted regarding the timing of combination therapies as well as to identify alternative combination regimens with comparable efficacy, patients are surviving longer because of these interventions. Yet, significant gaps in our knowledge remain that must be addressed to advance the field further.

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