Choice of Initial Oral Therapy for Pulmonary Arterial Hypertension: Age and Long-Term Survival

To the Editor:

Oral therapy is recommended for patients with low- or intermediate-risk pulmonary arterial hypertension (PAH) (1). Up-front combination therapy is currently favored on the basis of the AMBITION (Ambrisentan and Tadalafil in Patients with Pulmonary Arterial Hypertension) trial showing delayed PAH hospitalizations at the cost of increased side effects (2). However, comparative long-term survival outcome data are lacking, and the specific drug choice remains controversial. Thus, we aimed to determine which initial oral treatment is associated with better long-term survival. We also sought to ascertain baseline patient characteristics that might help predict response to one particular class of therapy.

We conducted a retrospective cohort study in patients with group 1 PAH initially treated with either an endothelin receptor antagonist (ERA) or a phosphodiesterase 5 inhibitor (PDE5i). We excluded patients in whom a second agent was added within 8 weeks. The primary outcome was all-cause mortality. Forty-three baseline variables considered as confounders (covariates) included demographics, comorbidities, vital signs, functional status, pulmonary function testing, echocardiographic data, right heart hemodynamics, and laboratory studies. For variables with missing data, we performed a single imputation using a random draw from the existing values, and we created a missingness indicator for the variables with at least 20 missing values. We adjusted for imbalances in these covariates by building propensity score models. We used a caliper matching algorithm to match, without replacement, each ERA patient to a PDE5i patient. We also used inverse propensity score weighting of the two groups. Excellent balance of the covariates was achieved. We then analyzed the outcome in the matched groups and also after including the propensity score weights and the linear propensity scores in the Cox models ("double robust" analysis). In the responder analyses, age, sex, race, and body mass index (BMI) were considered as potential effect modifiers of the initial PAH treatment. We built Cox models using treatment exposure; the linear propensity score; and product terms describing the interactions of age, sex, race, and BMI with treatment. All statistical analyses were performed with R version 3.3.2 (3).

Four-hundred fifty-four patients with PAH were examined for eligibility, and 217 were excluded (71 with no therapy documented, 52 with baseline data available only after therapy, 65 who received

other therapies, and 29 who did not meet hemodynamic criteria). A total of 237 patients were included, 91 initially treated with an ERA and 146 with a PDE5i. Table 1 depicts baseline characteristics of the population. In the ERA group, 81 (89%) received bosentan, and 5 (5.5%) each received ambrisentan and macitentan. In the PDE5i group, 121 (82.9%) were treated with sildenafil and 25 (17.1%) with tadalafil. At the end of follow-up, 44 (48.4%) ERA patients were receiving monotherapy, 32 (35.2%) were receiving double therapy, 14 (15.4%) were receiving triple therapy, and 9 (9.9%) were receiving parenteral prostacyclin. Among PDE5i patients, 79 (54.1%) were receiving monotherapy at last follow-up, 43 (29.5%) were receiving double therapy, 18 (12.3%) were receiving triple therapy, and 11 (7.5%) were receiving parenteral prostacyclin. All comparisons for medications at the end of follow-up were not significant. Patients were followed for a median of 1,304 (25th–75th percentiles, 606–2,058) days. There were 48 (52.7%) deaths in the ERA group and 71 (48.6%) in the PDE5i group. In the unadjusted analysis, initial treatment with an ERA had a borderline association with decreased mortality (hazard ratio [HR], 0.722; 95% confidence interval, 0.496–1.052; $P = 0.09$). After propensity score adjustment, there was no difference in mortality: The matched adjusted HR was 1.176 (0.616–2.246), and the double-robust adjusted HR was 0.876 (0.477–1.61). These results were not changed when adjusting these analyses for the proportion of patients receiving monotherapy throughout the study period, the use of parenteral prostacyclin, or the total number of PAH targeted therapies at the end of follow-up. There was no difference between groups in time to clinical worsening (defined as death, lung transplant, or PAH hospitalization) in the unadjusted or propensity score-adjusted analyses.

In a model adjusted for treatment exposure, sex, race, BMI, and the linear propensity score, there was a significant interaction between treatment exposure and age ($P = 0.002$). In patients older than 65 years of age, the relative hazard of death was higher for patients in the ERA group. In patients less than 45 years of age, the relative hazard of death was lower for patients in the ERA group. The differences were more pronounced in white women, the largest group in our study. In white women treated with an ERA, the HR for death for those younger than 45 years old was 0.43 (0.20–0.9; $P = 0.03$), whereas for those older than 65 years old, the HR was 1.80 (1.09–2.97; $P = 0.02$). Figure 1 shows representative survival curves according to treatment exposure after adjusting for age, sex, race, BMI, and linear propensity score. In a 40-year-old white woman, survival was better with ERA treatment. In a 70-year-old white woman, survival appeared slightly worse with ERA therapy. The interaction between treatment group and age remained significant ($P = 0.009$) after adjusting for treatment era, the presence of three or more heart failure with preserved ejection fraction risk factors (defined in Table 1 footnote), scleroderma, and the REVEAL (Registry to Evaluate Early and Long-Term PAH Disease Management) score.

The key findings of this study are that 1) there was no difference in long-term survival in patients with PAH initially treated with ERA monotherapy compared with PDE5i monotherapy, and 2) age was an important effect modifier, because ERA monotherapy as compared with PDE5i was associated with

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Table 1. Baseline Characteristics of the Study Population

	ERA (n = 91)	PDE5i (n = 146)	P Value
Age, yr, mean $\pm$ SD	54.1 $\pm$ 16.3	57.1 $\pm$ 15.5	0.158
Female sex, n (%)	75 (82.4)	91 (62.3)	0.002
Race/ethnicity, n (%)			0.257
White	77 (84.6)	115 (78.8)	
Black	11 (12.1)	23 (15.8)	
Other	3 (3.3)	8 (5.4)	
BMI, kg/m ² , mean $\pm$ SD	29.8 $\pm$ 7.5	29.6 $\pm$ 8.3 (n = 145)	0.823
PAH classification, n (%)			0.35
Idiopathic	37 (40.7)	60 (41.1)	
Heritable	1 (1.1)	8 (5.5)	
Connective tissue disease	38 (41.8)	53 (36.3)	
Congenital heart disease	15 (16.5)	25 (17.1)	
Scleroderma, n (%)	27 (29.7)	38 (26.0)	0.644
Treatment era, n (%)			<0.001
2001–2005	47 (51.6)	4 (2.7)	
2006–2010	29 (31.9)	82 (56.2)	
2011–2015	15 (16.5)	60 (41.1)	
Diabetes, n (%)	15 (16.5)	27 (18.5)	0.827
Hypertension, n (%)	48 (52.7)	81 (55.5)	0.782
Dyslipidemia, n (%)	21 (23.1)	50 (34.2)	0.093
COPD, n (%)	8 (8.8)	28 (19.2)	0.048
OSA, n (%)	17 (18.7)	30 (20.5)	0.855
ILD, n (%)	17 (18.7)	28 (19.2)	1
CAD, n (%)	11 (12.1)	29 (19.9)	0.169
Smoker, n (%)	33 (36.3)	64 (43.8)	0.309
CKD, n (%)	6 (6.6)	19 (13.0)	0.178
At least three HFpEF risk factors	9 (9.9)	28 (19.2)	0.08
<45 yr (n = 51)	1 (4.2)	2 (7.4)	1
>65 yr (n = 72)	(n = 24) 3 (11.5)	(n = 27) 15 (32.6)	0.09
Warfarin, n (%)	24 (26.4)	31 (21.2)	0.451
Oxygen therapy, n (%)	18 (19.8)	37 (25.3)	0.407
Resting oxygen saturation, %, median (25th–75th percentile)	95 (93–97) (n = 85)	96 (92–97.5) (n = 131)	0.738
NYHA classification, n (%)			0.393
I	4 (4.5)	3 (2.1)	
II	29 (33.0)	42 (28.8)	
III	47 (53.4)	79 (54.1)	
IV	8 (9.1) (n = 88)	22 (15.1)	
Systolic blood pressure, mm Hg, mean $\pm$ SD	136.5 $\pm$ 27.0 (n = 83)	128.3 $\pm$ 23.2 (n = 133)	0.018
Resting heart rate, beats/min, mean $\pm$ SD	81.1 $\pm$ 4.3 (n = 88)	80.6 $\pm$ 14.6 (n = 143)	0.836
6-min-walk distance, m, mean $\pm$ SD	329.0 $\pm$ 106.1 (n = 86)	293.5 $\pm$ 111.2 (n = 131)	0.02
Right ventricle dilation, n (%)	63 (70.0) (n = 90)	107 (74.3) (n = 144)	0.57
Pericardial effusion, n (%)	18 (20.0) (n = 90)	20 (14.0) (n = 143)	0.304
High natriuretic peptide, n (%)	49 (62.0) (n = 79)	76 (63.9) (n = 119)	0.91
Right heart hemodynamics			
RAP, mm Hg, mean $\pm$ SD	9.0 $\pm$ 5.5 (n = 88)	10.2 $\pm$ 6.5 (n = 139)	0.153
Mean PAP, mm Hg, mean $\pm$ SD	48.9 $\pm$ 14.2	47.0 $\pm$ 13.3	0.299
PAWP, mm Hg, median (25th–75th percentile)	10 (8–13) (n = 90)	11 (8–15) (n = 144)	0.09
Cardiac index, L/min/m ² , median (25th–75th percentile)	2.5 (2.1–2.9) (n = 81)	2.3 (2.0–2.8) (n = 140)	0.162

(Continued)

Table 1. (Continued)

	ERA (n = 91)	PDE5i (n = 146)	P Value
PVR, Wood units, median (25th–75th percentile)	8.0 (5.4–11.1) (n = 80)	7.7 (5.3–10.7) (n = 138)	0.358
DL _{CO} , %, mean ± SD	48.0 ± 20.6 (n = 70)	52.1 ± 24.7 (n = 117)	0.249
Creatinine, mg/dl, median (25th–75th percentile)	0.84 (0.70–1.06) (n = 90)	0.97 (0.78–1.20)	0.103
Sodium, mEq/L, mean ± SD	139.8 ± 3.3 (n = 90)	138.7 ± 3.4	0.039
REVEAL score, median (25th–75th percentile)	8 (6–10)	9 (6–10)	0.21

Definition of abbreviations: BMI = body mass index; CAD = coronary artery disease; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; ERA = endothelin receptor antagonist; HFpEF = heart failure with preserved ejection fraction (these risk factors included BMI ≥ 30 kg/m², hypertension, diabetes mellitus, and CAD); ILD = interstitial lung disease; NYHA = New York Heart Association; OSA = obstructive sleep apnea; PAH = pulmonary arterial hypertension; PAP = pulmonary artery pressure; PAWP = pulmonary artery wedge pressure; PDE5i = phosphodiesterase 5 inhibitor; PVR = pulmonary vascular resistance; RAP = right atrial pressure; REVEAL = Registry to Evaluate Early and Long-Term PAH Disease Management. Continuous variables are presented as mean $\pm$ SD when normally distributed and as median (25th–75th percentile) otherwise. Categorical variables are presented as counts and percentages.

decreased mortality in younger patients, whereas initial PDE5i monotherapy as compared with ERA monotherapy was associated with better survival in older patients.

We show, for the first time to our knowledge, that age modifies the response to two different forms of PAH targeted therapy, not compared with placebo. Furthermore, we show that early exposure to ERA or PDE5i leads to differences in long-term mortality, especially in young individuals. Previous studies have shown interactions between sex and race and response to ERA (4) or PDE5i (5) therapy when compared with placebo and measured by the walk test. A single-nucleotide polymorphism in the endothelin 1 pathway was associated with clinical improvements in patients of European descent treated with an ERA (6). More data are needed to be able to predict treatment responsiveness at the individual level.

Our study deals with the effects of initial monotherapy. In the AMBITION trial, no improvement in mortality was noted (2). In a *post hoc* analysis, a higher baseline cardiac index was predictive of increased mortality with up-front combination therapy (7). This

finding suggests that some patients with preserved baseline cardiac function may develop harmful elevations in cardiac index with combination therapy (8). Meta-analyses have documented the benefits of sequential add-on therapy in delaying the time to clinical worsening (9, 10).

Change in medical practice over the study period and sequential add-on PAH therapy could have affected the observed outcomes. However, our results did not change after adjusting our models for treatment era and follow-up medications. Unmeasured confounders, such as compliance with the prescribed therapy, are not accounted for. Occult heart failure with preserved ejection fraction in the elderly may account for worse outcomes with ERA therapy, but it does not explain the improved survival in young patients, the most striking difference observed in our study.

In conclusion, long-term survival was similar with initial treatment with an ERA or a PDE5i after adjusting for baseline covariates via propensity score methods. Younger people had better survival when treated with an ERA than when treated with a PDE5i.

Figure 1. Model-based representative adjusted survival curves for (A) a 40-year-old white woman and (B) a 70-year-old white woman, adjusted for body mass index and linear propensity score. Survival is significantly better in young patients treated with an ERA than in those treated with a PDE5i. ERA = endothelin receptor antagonist; PDE5i = phosphodiesterase 5 inhibitor.

These data provide support for a targeted approach to therapy, but more studies are needed to prove the efficacy and safety of this strategy. ■

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References

- Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, *et al*. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Respir J* 2015;46:903–975.
- Galiè N, Barberà JA, Frost AE, Ghofrani HA, Hoeper MM, McLaughlin VV, *et al*.; AMBITION Investigators. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. *N Engl J Med* 2015;373:834–844.
- RStudio Team. RStudio: integrated development environment for R. Boston: RStudio, Inc.; 2016.
- Gabler NB, French B, Strom BL, Liu Z, Palevsky HI, Taichman DB, *et al*. Race and sex differences in response to endothelin receptor antagonists for pulmonary arterial hypertension. *Chest* 2012;141:20–26.
- Mathai SC, Hassoun PM, Puhon MA, Zhou Y, Wise RA. Sex differences in response to tadalafil in pulmonary arterial hypertension. *Chest* 2015;147:188–197.
- Benza RL, Gomberg-Maitland M, Demarco T, Frost AE, Torbicki A, Langleben D, *et al*. Endothelin-1 pathway polymorphisms and outcomes in pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2015;192:1345–1354.
- Hoeper MM, McLaughlin VV, Barberà JA, Frost AE, Ghofrani HA, Peacock AJ, *et al*. Initial combination therapy with ambrisentan and tadalafil and mortality in patients with pulmonary arterial hypertension: a secondary analysis of the results from the randomised, controlled AMBITION study. *Lancet Respir Med* 2016;4:894–901.
- Hassoun PM. Time to consider death in clinical trials for PAH. *Lancet Respir Med* 2016;4:849–850.
- Fox BD, Shtraichman O, Langleben D, Shimony A, Kramer MR. Combination therapy for pulmonary arterial hypertension: a systematic review and meta-analysis. *Can J Cardiol* 2016;32:1520–1530.
- Lajoie AC, Lauzière G, Lega JC, Lacasse Y, Martin S, Simard S, *et al*. Combination therapy versus monotherapy for pulmonary arterial hypertension: a meta-analysis. *Lancet Respir Med* 2016;4:291–305.

Safety of Extubating Mechanically Ventilated Patients Receiving Vasoactive Infusions: A Retrospective Cohort Study

To the Editor:

Discontinuation of vasopressors or inotropes is a common precondition for spontaneous breathing trials or extubation in U.S. clinical trials and guidelines (1–4). A contrary view is that such a delay increases patients' risks for the complications of endotracheal intubation and mechanical ventilation (5) and may mandate additional ICU time, decreasing throughput and effective ICU capacity (6).

The Glasgow Royal Infirmary ICU extubates select patients while on vasopressors/inotropes (“vasoactive infusions”), but the safety of this procedure has never been formally evaluated. We asked, “Among intubated patients who ever receive vasoactive infusions, are extubations attempted whilst patients are still on vasoactive infusions associated with different ICU mortality (primary outcome) than extubations attempted after the infusions have been stopped?” Secondary outcomes included reintubation, hospital mortality, and ICU and hospital lengths of stay.

The Glasgow Royal Infirmary ICU is a 20-bed mixed medical/surgical ICU with tertiary referrals for burn, upper gastrointestinal, and pancreatic care. It does not have cardiothoracic services on site and does not routinely admit elective surgery patients with an uneventful intraoperative course. Neither an extubation protocol nor formal spontaneous breathing trials are routinely used. Clinical practice is to extubate patients—at the attending physician's discretion—who have minimal ventilatory and oxygen support, an adequate cough, and ideally are able to participate in physiotherapy.

This retrospective study included all patients intubated from January 2007 to February 2017 who received a vasoactive infusion while intubated. Each patient's first extubation attempt was analyzed because patients who have previously failed an extubation are managed in different ways. We did not include readmissions in the same hospital episode, and ICU death was defined as death arising from the index ICU admission. Patients receiving 0 to 0.1 mg/h of noradrenaline, adrenaline, metaraminol, or dobutamine at the time of their extubation were excluded ($n = 43$) because this is a marginal dose. Also excluded were those who died before a first extubation attempt, self-extubated ($n = 4$), and were extubated explicitly onto a palliative care pathway ($n = 6$). De-identified data were extracted from operational electronic data systems. Data were analyzed in R version 3.4.3 (R Core Team 2017). Continuous variables were

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