PHA 2022 International Pulmonary Hypertension Conference Abstracts

BOSENTAN DECREASES RIGHT VENTRICULAR SYSTOLIC PRESSURE AND PRO-BRAIN NATRIURETIC PEPTIDE LEVELS IN INFANTS WITH PULMONARY HYPERTENSION

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Category: Clinical Science
Selected Areas: Pediatrics, Therapeutic Strategies

Background: Pulmonary hypertension (PH) is a rare and potentially fatal disease in children if left untreated. Emerging therapies, including bosentan, a dual endothelin receptor antagonist (ERA), have shown significant benefits in the adult PH population; however, few studies have assessed the efficacy and safety of ERAs in infants and young children.
Methods: Our study was a single-center retrospective analysis of patients <2 years of age with a confirmed diagnosis of PH and started on bosentan therapy between 2017 and 2020. Twelve cases met eligibility criteria. Demographic (Table 1), laboratory, echocardiographic, and cardiac catheterization data were analyzed (Tables 2–4).
Results: With treatment, there was a statistically significant decrease in mean right ventricular systolic pressure estimated by the tricuspid regurgitation jet (79 ± 23 mm Hg reduced to 52 ± 25 mm Hg; *P* value <0.001) and pro-brain natriuretic peptide levels (21071 reduced to 2037; $P < 0.001$). Additionally, improvement and eventual normalization of right ventricular function and septal geometry was seen within the first 4 months of therapy (Figure). Patients who underwent cardiac

Table 1. Descriptive Statistics

Patient characteristic	Value (n = 12)[a]
Male	9 (75)
Female	3 (25)
Gestational age at birth, wk	31.8 ± 6 (23.4–40)
Birth weight, g	1759 ± 1106 (660–3580)
Ethnicity	
African American	7 (58)
Caucasian	5 (42)
Etiology of PH, mo	
Chronic lung disease alone	1 (8)
Congenital heart disease alone	1 (8)
Mixed lung and heart disease	10 (83)
Age at diagnosis, mo	3.6 ± 2.4 (0–7.2)
Age at time of bosentan initiation, mo	9.6 ± 4.4 (3–17.8)
Time from diagnosis to initiation of bosentan therapy, mo	6.0 ± 5.2 (0.3–17.8)
ICU survival	7 (58)
Hospital survival	7 (58)

ICU, intensive care unit; PH, pulmonary arterial hypertension.
[a]Data are shown as n (%) or mean ± SD (range).

Table 2. Change in Echocardiographic Parameters with Treatment

Parameter	Baseline (n = 12)[a]	Posttreatment (n = 11[b])	*P*value
Right ventricular function			
Normal	6 (50)	11 (100)	0.04
Mildly depressed	4 (33)	0 (0)	<0.01
Moderately depressed	2 (17)	0 (0)	<0.01
Interventricular septal position			
Normal	0 (0)	4 (36)	0.09
Flat in systole	2 (17)	3 (27)	1.00
Flat in diastole	0 (0)	1 (10)	1.00
Flat in systole and diastole	5 (42)	3 (27)	0.66
Bowing into the left ventricle in systole	5 (42)	0 (0)	0.04
RVSP from TR, mm Hg	79 ± 23 (40–120)	52 ± 25 (23–100)	<0.001
Left ventricular ejection fraction, %	77 ± 10 (58–88)	71 ± 9.6 (59–88)	0.50

RVSP, right ventricular systolic pressure; TR, tricuspid regurgitation jet.
[a]Data are shown as n (%) or mean ± SD (range).
[b]One patient died prior to getting a posttreatment echocardiogram.

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Table 3. Change in Catheterization Parameters with Treatment

	Baseline (n = 7)[a]	Posttreatment (n = 4)	*P* value	95% confidence interval
Parameters				
PVRi (Wood units × m^2)	5.06	3.14	0.140	–0.77 to 4.62
SVRi (Wood units × m^2)	10.7	11.4	0.811	–7.80 to 6.27
PVR/SVR ratio	0.54	0.34	0.253	–0.17 to 0.57
Mean pulmonary artery pressure, mm Hg	34.4	31.0	0.443	–5.67 to 12.9
Diastolic pulmonary pressure, mm Hg	21.0	16.0	0.018	1.06–8.94
Transpulmonary gradient, mm Hg	23.7	18.7	0.183	–2.79 to 12.8
Diastolic pulmonary gradient, mm Hg	9.5	7.0	0.403	–3.87 to 8.87

PVRi, indexed pulmonary vascular resistance; PVR/SVR, pulmonary vascular resistance to systemic vascular resistance; SVRi, indexed systemic vascular resistance.

[a]Data are shown as mean values.

Table 4. Change in Laboratory Values with Treatment

Laboratory value	Baseline (n = 12)[a]	Posttreatment (n = 12)	*P* value	95% confidence interval
Pro-BNP	21071	2037	<0.001	4655–33413
Hemoglobin	11.09	11.95	0.161	–2.07 to 0.36
Platelet count	269.75	259.24	0.732	–51.3 to 72.3
AST	52.1	45.54	0.359	–7.78 to 20.9
ALT	43.3	32.96	0.137	–3.46 to 24.1

ALT, alanine aminotransferase; AST, aspartate transaminase; Pro-BNP, pro-brain natriuretic peptide.

[a]Data are shown as n (%) or mean ± SD (range).

catheterization after therapy initiation (n = 4) demonstrated hemodynamic improvements; however, only the decrease in diastolic pulmonary pressure was statistically significant (*P* value = 0.018). No significant difference in hemoglobin, platelet count, or liver function tests was observed between groups.

Conclusions: In conclusion, these data suggest that bosentan may be an effective and relatively safe treatment option for children <2 years of age with PH. Further long-term randomized control studies are necessary to validate the potential clinical benefit of using this drug therapy in young children.

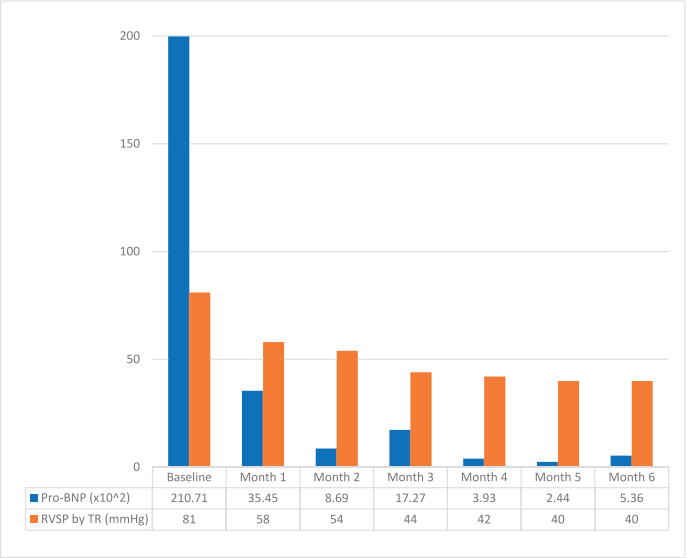

Figure 1: Pro-brain natriuretic peptide and right ventricular systolic pressure trends by month. Pro-BNP, pro-brain natriuretic peptide; RVSP, right ventricular systolic pressure; TR, tricuspid regurgitation jet.

CONCOMITANT MEDICATION USE IN TREATMENT JOURNEY OF PULMONARY ARTERIAL HYPERTENSION PATIENT: A CANADIAN RETROSPECTIVE CLAIMS ANALYSIS

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Selected Areas: Databases and Registries

Background: The current standard of care for pulmonary arterial hypertension (PAH) is combination therapy, which imposes pill burden on PAH patients who live with multiple comorbidities. This study aims to understand the concomitant medication use in treatment journey of Canadian PAH patients.

Methods: Patients initiating PAH therapy (index) from September 1, 2016, to August 31, 2019, were selected in the Ontario Drug Benefits (ODB), Régie de l'assurance maladie du Québec (RAMQ), and IQVIA Canadian Private Drug Plan (PDP) databases. Medication prescriptions 5-year prior and 1-year postindex were tracked. Concomitant medication

analysis used ODB and PDP; prescriber specialty analysis used PDP database.
Results: A total of 1019 patients were included from ODB (N = 481), PDP (N = 422), and RAMQ (N = 116). Tadalafil (61%) and sildenafil (22%) were most prescribed at index. One year prior to index, 75% and 30% of patients with concomitant medications (N = 828) were on 5+ and 10+ concomitant medication classes, respectively. From 5 years prior to the 1-year postindex, the proportion of cardiovascular medications use declined (16% versus 13%), while that of diuretics use increased (10% versus 16%). Compared with the year prior, prescriptions of rescue treatment decreased 1 year postindex (926 versus 763). Here, 72% of patients (N = 300) were prescribed by general practitioner (GP) before index, while prescribers of cardiovascular and respiratory medications shifted from GP to specialist postindex. Among the top 3 prescribers, females had a significant reduction in the number of concomitant medications postindex, while males trended the opposite way.
Conclusions: This study shows the complex treatment journey of Canadian PAH patients and highlights the need to reduce pill burden and improve disease management.

WORLD DRUG RETENTION AND INITIATION OF COMBINATION DRUG THERAPY FOR PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION IN CANADA

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Category: Clinical Science
Selected Areas: Databases and Registries

Background: Treatment guidelines for pulmonary arterial hypertension (PAH) recommend combination therapy in most patients. This study evaluated retention of PAH drugs and time-to-initiation of combination drug therapy with macitentan and selexipag in Canada.
Methods: Patients claiming PAH drugs from January 2017 to March 2021 were identified in the Ontario Drug Benefits (ODB), Régie de l'assurance maladie du Québec (RAMQ), and IQVIA Canadian Private Drug Plan (PDP) databases. Drug retention was calculated for patients submitting claims 12 months following treatment index (March 2019 to February 2020 [PDP, ODB]; January to December 2019 [RAMQ]). Treatment was considered first line if patients were treatment naïve with >180 days of claims history. Time-to-initiation of combination therapy was calculated for macitentan+PDE5i and selexipag-containing therapies.
Results: Around 2150 patients claimed PAH drugs annually, with averages of 1000 (PDP), 900 (ODB), and 250 (RAMQ). Most patients were female (65%–77%) and aged 45+ years (69%–85%). The 12-month retention was greatest for macitentan in PDP (67%) and RAMQ (88%), and tadalafil (78%) in ODB. Of patients on macitentan or selexipag, approximately 79% and 95% were on combination therapy (2+ drugs) in 2020, respectively. In 2020, 12%–17% of patients were on macitentan combination therapy (3+ drugs), and 43%–69% were on selexipag combination therapy (3+ drugs). In 2020, mean time-to-initiation was 4–5 months for macitentan+PDE5i and 17–23 months for selexipag-containing therapies (Table).
Conclusions: Real-world data from Canada shows that most PAH patients on macitentan or selexipag are on combination therapies. Time-to-initiation was 4–5 months for macitentan+PDE5i, and 17–23 months for selexipag-containing combination therapies. This study shows the complex treatment journey of Canadian PAH patients and highlights the need to reduce pill burden and improve disease management.

Table 1. Annual Average Time (mo) From First-Line PAH Treatment to Selexipag- and Macitentan-Combination Therapy, 2017–2021

	Selexipag combination therapy			Macitentan combination therapy	
Source	ODB	PDP	RAMQ	PDP	RAMQ
2017	N/A	17.0	16.5	6.8	4.4
2018	24.0	21.0	18.7	4.3	3.0
2019	24.3	17.0	28.2	4.3	3.1
2020	17.8	17.0	22.8	5.1	4.2
2021 YTD	30.3	19.0	15.5	7.4	4.6

RATIONALE AND DESIGN OF THE RIOCIGUAT USERS (ROAR) REGISTRY

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Category: Clinical Science
Selected Areas: Databases and Registries, Quality of Life, Therapeutic Strategies

Background: Initial pulmonary arterial hypertension (PAH) treatment has evolved from monotherapy to combinations of approved drug classes. Riociguat was approved for PAH based on the PATENT study, which studied it as monotherapy or in sequential combination with an endothelin receptor antagonist (ERA) or nonparenteral prostanoid. PATENT and REPLACE gave substantial data on riociguat combinations, but there are no US-based registry data on riociguat.
Methods: ROAR (NCT04813926; funder: Bayer US, LLC) is a US-based, multicenter, prospective, observational registry of adults with PAH who are riociguat-naïve or who initiated riociguat 90 days previously. Data will be collected at standard-of-care visits (usually every 3–6 months) for 24 months or until 30 days after discontinuing riociguat. Planned enrollment: 500 patients (~50 sites). The primary objective is to study safety and effectiveness of riociguat as first-line therapy or combined with an ERA and/or prostanoid. Secondary objectives include safety and effectiveness of first-line riociguat versus transition from a phosphodiesterase-5 inhibitor, and the importance of treatment sequence. Effectiveness outcomes include change from baseline to months 6 and 12 in 6-minute walk distance, biomarkers, clinical PAH risk scores, hemodynamics (right heart catheterization), echocardiography, laboratory tests, and New York Heart Association and World Health Organization functional class. Patient-reported outcomes will be assessed at baseline, month 6, and month 12. Primary safety endpoints are incidence of selected adverse events and serious adverse events through 24 months. ROAR began recruitment in July 2021.
Results: By January 13, 2022, 35 patients were enrolled.
Conclusions: Interim baseline data will be presented.

UNDERSTANDING DRIVERS AND BARRIERS TO PARTICIPATION IN CLINICAL TRIALS FOR PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION

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Category: Clinical Science
Selected Areas: Databases and Registries

Background: Ongoing trials of therapies targeting drivers of disease are key to improving outcomes in patients with pulmonary arterial hypertension (PAH), but enrollment is challenging. Factors affecting enrollment in PAH trials are not well characterized. We conducted a survey to identify factors that encourage or discourage trial participation by PAH patients.
Methods: A survey was administered through Rare Patient Voice, an online platform used by >100 000 patients and

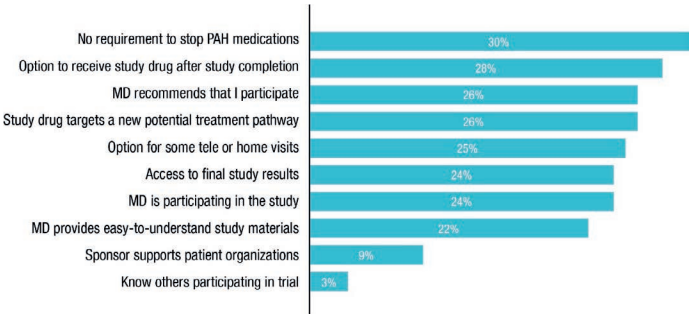

Figure 1: Top factors encouraging participation in clinical trials.

caregivers, to gather demographics, trial considerations, and preferences for health care provider (HCP) communication. Eligible participants were >21 years old, treated with 1 PAH medication, had a self-reported PAH diagnosis for 6 months, and had never participated in a clinical trial. The protocol was approved by a central institutional review board, and participants provided informed consent.

Results: One hundred two patients completed the survey. Average age was 51.4 years, average time from PAH diagnosis was 8.3 years, and 69% reported stable disease. Fifty-three percent and 37% of respondents were *very interested* and *somewhat interested* in trial participation, respectively, yet 75% reported not having a discussion about trial participation with HCPs. Over 90% reported they would welcome such a discussion. Factors encouraging trial participation are summarized (Figure).

Conclusions: While PAH patients are interested in clinical trial enrollment, awareness regarding trial opportunities is lacking. Other barriers to participation include concerns regarding maintenance of current therapy and providers and a desire to continue study drug after trial completion. Further education is needed for patients and clinicians to encourage trial participation.

IMPROVING THE USE OF RISK ASSESSMENTS FOR PULMONARY ARTERIAL HYPERTENSION: A QUALITY IMPROVEMENT INITIATIVE AT A PULMONARY HYPERTENSION SPECIALTY CLINIC

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Category: Clinical Science
Selected Areas: Therapeutic Strategies

Background: The most recent pulmonary arterial hypertension (PAH) guidelines stress the importance of multiparameter risk assessments to classify disease severity and guide management decisions. However, formal risk assessment tools are often underused in clinical practice, leading to missed op-

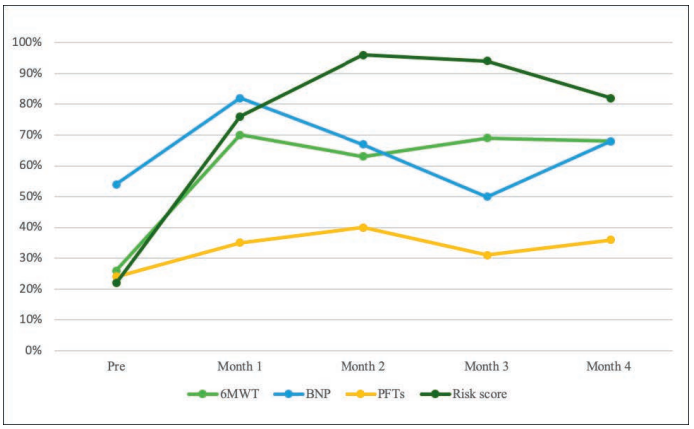

Figure 1: Risk assessment and variable documentation by month.

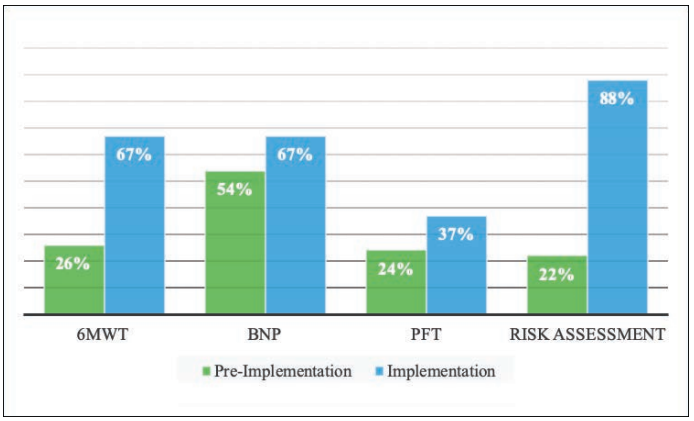

Figure 2: Chart audit results.

portunities to escalate pharmacotherapy and other supportive measures, which may prevent clinical deterioration.
Methods: A retrospective chart review was conducted to understand the frequency of risk assessment documentation at a large pulmonary hypertension (PH) specialty clinic. Electronic medical record (EMR) modifications, including a REVEAL 2.0 flowsheet and quick text, were implemented to support provider use of a formal risk assessment tool. An education session for providers focused on the new EMR features and the collection of key variables necessary for accurate risk assessments. A separate training for medical assistants reviewed the organization's 6-minute walk test (6MWT) protocol. Throughout the project period, audit and feedback cycles were used to measure and communicate progress toward outcome objectives.
Results: During the 4-month implementation period, documentation of risk assessments improved from 22% to 88%. The percent of patients with a 6MWT documented in the previous 6 months increased from 26% to 67%. The collection of brain natriuretic peptide values and pulmonary fitness tests also improved (Figures 1 and 2).
Conclusions: EMR integration of a preferred risk assessment tool paired with evidence-based quality improvement methods is an effective strategy to increase provider use of PAH risk assessments in a real-world setting. More research is needed to understand how this increased collection of risk assessments affects management decisions. The effects of risk stratification on the selection and timing of pharmacotherapy is of particular interest.

CASE STUDIES ON OUTCOME OF CONGENITAL HEART DEFECTS ATTRIBUTED TO TIMING OF SCREENING AND INTERVENTION

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Category: Case Report
Selected Areas: Diagnosis or Screening and Physiologic Studies; Diseases and Conditions Associated with PH; Quality of Life

Background: Congenital heart defects (CHDs) are the most common types of birth defects (1% of births per year in the United States). Among babies with CHD, 1 in 4 presents critical CHD with a need for surgery in infancy. In this study, we highlight the importance of screening camp and early intervention in pulmonary arterial hypertension (PAH) cases secondary to CHDs in rural settings of Nepal.
Methods: Series of comprehensive cardiac screening camps were conducted in different parts of rural Nepal. In this paper, we present clinical symptoms, diagnosis, surgical management, and follow-up outcomes of 2 PAH cases secondary to CHD who were screened at one of the cardiac camps and referred to and reevaluated in tertiary cardiac centers.
Results: The first case of an 11-year-old female who was referred from the screening camp was managed surgically in 37 days of screening, had a favorable outcome, and was doing well during follow-up, whereas the second case of a 22-year-old male managed surgically after 9 months of screening had an unfavorable outcome of death on the first postoperative day. The difference in time to surgical management in both cases was attributed to several factors: patient's age, awareness and their socioeconomic factors, and clinical heterogeneity in consensus recommendation and practices in government facilities in Nepal.
Conclusions: Cardiac screening camp in rural settings of developing countries like Nepal may help in early diagnosis and prevention of cardiac related morbidity and mortality. Early diagnosis and hence management of CHD facilitated through cardiac screening camp can save many more lives of children living with CHDs if conducted effectively with continuity of care at regular follow-up intervals.

PHASE 1, OPEN-LABEL STUDY OF INHALED SERALUTINIB TO ASSESS POTENTIAL EFFECTS ON THE PHARMACOKINETICS OF CYTOCHROME P450 AND TRANSPORTERS

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Category: Clinical Science
Selected Areas: Therapeutic Strategies

Background: Seralutinib is an inhaled small-molecule kinase inhibitor specifically developed for the treatment of pulmonary arterial hypertension (PAH), with an optimized kinase specificity profile that targets PDGFRa/β, CSF1R, and c-KIT, and modulates BMPR2. Targeting these pathways may reverse pulmonary vascular inflammation, cellular proliferation, and fibrosis. In addition, by directly targeting the diseased lung, inhaled seralutinib limits systemic exposure. Based on in vitro predictions and given that multi-agent regimens are often required in treating PAH, we evaluated the potential for drug-drug interactions (DDIs) with inhaled seralutinib.
Methods: Twenty-four healthy adults received a cocktail of probe substrates: caffeine (CYP1A2), montelukast (CYP2C8), flurbiprofen (CYP2C9), midazolam (CYP3A), digoxin (P-gp), and pravastatin (OATP1B1/1B3) with or without seralutinib. Pharmacokinetics and safety were evaluated.
Results: Geometric least square mean ratios for Cmax and AUC of probe substrates with and without seralutinib are shown. Seralutinib is a moderate CYP3A inhibitor per the effect on midazolam (Figure).
Conclusions: Based on the moderate effect, seralutinib is not expected to cause clinically relevant DDIs with most PAH drugs that are CYP3A substrates (tadalafil, riociguat, bosentan, and macitentan); these drugs may be co-administered without dose modification. In the case of sildenafil, dose adjustments should be considered based on risk-benefit assessment. In addition, clinically relevant DDIs with substrates of CYP1A2, CYP2C8, CYP2C9, CYP2C19, P-gp (except for digoxin), or OATP1B1/1B3 are not anticipated. Seralutinib was well tolerated with or without co-administered agents.

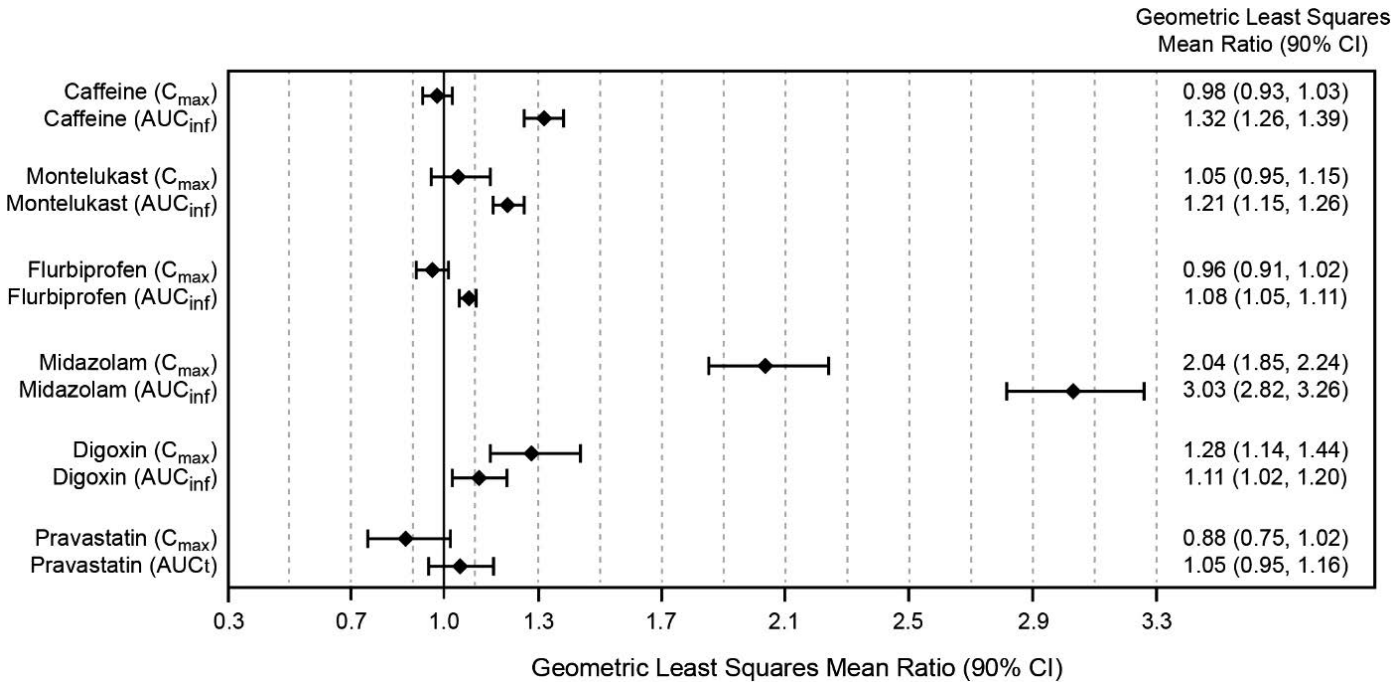

Figure 1: Forest plot of geometric least square (LS) mean ratios of plasma pharmacokinetics (PK) parameters of probe substrates and metabolites (PK population).

EVIDENCE OF TARGET ENGAGEMENT AND PATHWAY MODULATION: BIOMARKER ANALYSIS OF THE PHASE 1B INHALED SERALUTINIB STUDY

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Category: Clinical Science
Selected Areas: Therapeutic Strategies

Background: Seralutinib is an inhaled small-molecule kinase inhibitor which selectively targets PDGFRa/β, CSF1R, and c-KIT signaling implicated in pulmonary arterial hypertension (PAH) pathobiology. An approximately 30× higher lung than plasma exposure and extended lung target engagement (TE) in preclinical studies suggest that pharmacodynamic activity in the human lung is expected at the dose levels studied. We evaluated changes in exploratory peripheral biomarkers of TE and mechanism of action in PAH subjects.
Methods: In a phase 1b multicenter, randomized, placebo-controlled study, subjects with PAH were randomized 3:1 to receive inhaled seralutinib up to 90 mg BID or placebo for 14 days. Whole blood and serum samples were collected at screening and day 14 for biomarker analysis: pretreatment, 5 minutes, and 2 hours posttreatment. A novel whole blood CSF1R internalization assay was developed to assess TE. Epigenetic immunoprofiling assays and RNAseq were performed.
Results: Eight subjects received seralutinib (n = 6) or placebo (n = 2). Seralutinib was well tolerated at doses up to 90 mg BID. Seralutinib inhibited CSF1R internalization at 5 minutes but not 2 hours postinhalation relative to baseline, consistent with its short half-life in peripheral circulation. Transcriptomics data at day 14 identified treatment-associated shifts in 779 genes. An epigenetic signal suggestive of increasing FOXP3+ Tregs:CD4+ T cells following treatment was also observed.
Conclusions: Preliminary biomarker findings support TE and downstream effects in the periphery that suggest target modulation by seralutinib in PAH patients. Seralutinib is being evaluated as a new treatment for patients with PAH receiving standard of care (SOC) background therapies in a recruiting phase 2 study (NCT04456998).

A PHASE 2 STUDY TO EVALUATE THE EFFICACY AND SAFETY OF INHALED SERALUTINIB FOR THE TREATMENT OF PULMONARY ARTERIAL HYPERTENSION: A TRIAL IN PROGRESS

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Category: Clinical Science
Selected Areas: Therapeutic Strategies

Background: Seralutinib is a potent, clinical-stage kinase inhibitor for treatment of patients with pulmonary arterial hypertension (PAH). It selectively targets PDGFRa/β, CSF1R, and c-KIT signaling implicated in PAH pathobiology, and modulates BMPR2. Seralutinib is delivered with a discreet, hand-held dry powder inhaler to directly target the diseased lung to limit systemic exposure and thereby potentially improve efficacy and tolerability. A phase 2 study is ongoing (TORREY; NCT04456998).

Methods: TORREY is a randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of inhaled seralutinib in adult subjects with World Health Organization Group 1 pulmonary hypertension (PH). Patients with Functional Class II or III PAH on therapy with a pulmonary vascular resistance (PVR) ≥400 dyn·s/cm^5 are eligible. The planned treatment period is 24 weeks, with a target enrollment of 80 patients. The primary endpoint is change in PVR measured by right heart catheterization from baseline to 24 weeks. The key secondary endpoint is change in 6-minute walk test (6MWT) from baseline to 24 weeks. Two substudies will explore novel endpoints. In the heart rate monitoring substudy, the effect of seralutinib on cardiac effort during 6MWT will be assessed. The computerized tomography substudy will examine the effect of seralutinib on pulmonary vascular remodeling by quantifying changes in pulmonary arterial blood volume. Exploratory biomarkers will be evaluated for target engagement and response to treatment.
Conclusions: This abstract was previously presented at the ISHLT2021 Annual Meeting and Scientific Sessions (Frantz et al., *J Heart Lung Transplant*. 2021;40(4 Suppl):S107. doi:10.1016/j.healun.2021.01.346).

CASE STUDY: PORTOPULMONARY HYPERTENSION

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Category: Case Report
Selected Areas: Diseases and Conditions Associated with PH

Background: Portopulmonary hypertension is pulmonary arterial hypertension (PAH) in portal hypertension. Pulmonary hypertension (PH) is classified in five groups: Group 1 is PAH with several etiologies including idiopathic, heritable PAH, collagen vascular disease, congenital heart disease, HIV, drugs, or portopulmonary hypertension. Group 2 is PH owing to left heart disease. Group 3 is PH owing to lung disease. Group 4 is chronic thromboembolic PH (CTEPH). Group 5 is miscellaneous cause of PH.
Methods: Portal hypertension develops in the setting of cirrhosis, extrahepatic portal vein thrombosis, or schistosomiasis. This results in the resistance to portal blood flow leading to complications such as ascites and variceal bleed. Portopulmonary hypertension affects up to 6% of patients with advanced liver disease.
Results: (Case) A 66-year-old woman with newly diagnosed PH World Symposia on Pulmonary Hypertension Group 1 with history of chronic Hepatitis C (HCV; status post Epclusa February through August 2020) and alcohol-related cirrhosis complicated by ascites and hepatopulmonary syndrome, hypertension, and diabetes type 2 was being evaluated for liver transplant. She had an echocardiogram which showed moderate PH. She was then referred after cardiac catheterization which showed systemic level PH. She was started on AMBITION medications with subsequent severe migraine headaches. She had gained fluid weight and was then admitted for further management.

PATIENT-REPORTED VERSUS CLINICIAN-ASSESSED FUNCTIONAL CLASS IN THE ADAPT PULMONARY ARTERIAL HYPERTENSION REGISTRY

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Table 1. Comparison of World Health Organization Functional Classification (WHO-FC; Completed by Clinician) and Pulmonary Hypertension Functional Classification Self-Report (PH-FC-SR; Completed by Patient)

	WHO-FC (Completed by clinician)	PH-FC-SR[1] (Completed by patient)
Class I	Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain or near syncope.	I have pulmonary hypertension, but my physical activity is not limited. I can do my day-to-day physical activity (e.g. household tasks, go to work, go to the store) and my usual exercise without getting short of breath or feeling tired or experiencing chest pains or feeling like I may faint.
Class II	Patients with pulmonary hypertension resulting in a slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope.	I have pulmonary hypertension and my physical activity is slightly limited. I feel comfortable at rest. I can do my day-to-day physical activity (e.g. household tasks, go to work, go to the store) but it makes me feel short of breath or tired or have chest pains or feel like I may faint.
Class III	Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain or near syncope.	I have pulmonary hypertension and my physical activity is noticeable limited. I feel comfortable at rest. I can do the type of physical activity I have to do on a day-to-day bases (e.g. bathing, dressing, preparing meals) but it makes me feel short of breath or tired or have chest pains or feel like I may faint.
Class IV	Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.	I have pulmonary hypertension and almost any physical activity makes me feel short of breath or tired or have chest pains or nearly faint. I frequently experience swollen ankles. I may have a bloated stomach. I may get short of breath or tired even when resting. I experience increasing amounts of discomfort with any physical activity.

[1]Highland KB, Crawford R, Classi P, et al. *Health Qual Life Outcomes.* 2021;19(1):202. Published 2021 Aug 24.

Table 2. Baseline Characteristics of Patients in Pulmonary Hypertension Functional Classification Self-Report (PH-FC-SR) Substudy From the ADAPT Registry

Patient Characteristics	n = 18
Age, mean (S.D.)	65 (15.2) years
Female sex – no. (%)	12 (67%)
Race/Ethnicity – no. (%)	
White	15 (83%)
Black/African American	2 (11%)
Asian	1 (6%)
Highest level of education– no. (%)	
High school diploma or equivalent	3 (17%)
Some college, no degree	5 (28%)
Associate degree	2 (11%)
Bachelor's degree	5 (28%)
Master's degree	1 (6%)
Professional or doctoral degree (PhD, MD, JD, PharmD, etc.)	1 (6%)
Prefer not to answer	1 (6%)
Working status at baseline – no. (%)	
Working full-time (≥40 hours per week)	6 (33%)
Working part-time (<40 hours per week)	3 (17%)
Disabled, permanently or temporarily	6 (33%)
Retired	3 (17%)
Time since PAH diagnosis, mean (S.D.)	5.7 (3.6) years
PAH classification – no. (%)	
Idiopathic	11 (61%)
Associated with connective tissue disease	4 (22%)
Associated with drug or toxin exposure	2 (11%)
Heritable	1 (6%)
PAH background medications – no. (%)	
None	4 (22%)
ERA only	2 (11%)
PDE-5i / sGCS only	3 (17%)
ERA + PDE-5i / sGCS	9 (50%)
6MWD at baseline, mean (S.D.)	424.1 (100) m
BNP at baseline, mean (S.D.) (n = 9)	107.4 (144.0) pg/mL
NT-proBNP at baseline, mean (S.D.) (n = 8)	1221.1 (1431.0) pg/mL

Note: table includes only patients with matched assessments of PH-FC-SR and WHO-FC.

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Category: Clinical Science
Selected Areas: Databases and Registries, Diagnosis or Screening and Physiologic Studies, Diseases and Conditions Associated with PH

Background: The World Health Organization Functional Classification (WHO-FC) measures pulmonary arterial hypertension (PAH) symptom severity and activity limitations. The Pulmonary Hypertension Functional Classification Self-Report (PH-FC-SR) is an adapted version of the WHO-FC for patient self-completion (Table 1). PH-FC-SR can provide longitudinal monitoring when collecting clinician-rated FC may not be feasible or practical. The study aimed to determine if patient-reported PH-FC-SR agreed with clinician-assessed WHO-FC.
Methods: ADAPT is a real-world registry of PAH patients taking oral treprostinil. An optional substudy in ADAPT collected PH-FC-SR and WHO-FC at baseline, week 24, and week 52. Patient responses were blinded to study team members assessing WHO-FC. PH-FC-SR and WHO-FC were matched if both patient and clinician completed the FC survey within 30 days of each other. Agreement between PH-FC-SR and WHO-FC was assessed.
Results: There were 27 matched assessments from 18 unique patients at 9 sites. Baseline characteristics include socioeconomic and PAH disease statuses (Table 2). Twenty-four of 27 (89%) matched assessments were completed on the same day (Table 3). Twenty-three of 27 (85%) patient and clinician scores were the same. Two patients underreported and 2 patients overreported PH-FC-SRs compared with matched clinician assessments

(unique patients, Table 3).

Conclusions: This is the first study assessing agreement between WHO-FC and PH-FC-SR. Patients from different sites with a range of PAH disease and socioeconomic statuses successfully matched clinician-assessed FC reports, supporting validity of use in clinical practice for longitudinal, at-home monitoring.

Table 3. Matched Patient-Reported Pulmonary Hypertension Functional Classification Self-Report (PH-FC-SR) and Clinician-Assessed World Health Organization Functional Classification (WHO-FC) Survey Responses. Discordant Assessments Are Italicized and Bolded

Observation #	Patient	Patient-Reported (PH-FC-SR)	Clinician-Assessed (WHO-FC)	Time between surveys (days)	Time of Assessment
1	A	CLASS III	CLASS III	0	Baseline
2	B	CLASS II	CLASS II	0	Baseline
3	B	CLASS II	CLASS II	0	Follow Up 1
4	***C***	***CLASS II***	***CLASS I***	***7***	***Baseline***
5	C	CLASS I	CLASS I	0	Follow Up 1
6	***D***	***CLASS II***	***CLASS III***	***0***	***Baseline***
7	E	CLASS II	CLASS II	0	Baseline
8	F	CLASS II	CLASS II	0	Baseline
9	***F***	***CLASS IV***	***CLASS II***	***0***	***Follow Up 1***
10	G	CLASS II	CLASS II	0	Baseline
11	H	CLASS II	CLASS II	16	Baseline
12	I	CLASS I	CLASS I	0	Baseline
13	I	CLASS I	CLASS I	0	Follow Up 1
14	I	CLASS I	CLASS I	0	Follow Up 2
15	J	CLASS II	CLASS II	0	Baseline
16	***K***	***CLASS III***	***CLASS IV***	***0***	***Baseline***
17	L	CLASS II	CLASS II	0	Baseline
18	L	CLASS II	CLASS II	0	Follow Up 1
19	M	CLASS II	CLASS II	0	Baseline
20	M	CLASS II	CLASS II	0	Follow Up 1
21	N	CLASS I	CLASS I	0	Baseline
22	O	CLASS I	CLASS I	0	Baseline
23	P	CLASS I	CLASS I	0	Baseline
24	P	CLASS I	CLASS I	0	Follow Up 2
25	Q	CLASS II	CLASS II	0	Baseline
26	Q	CLASS II	CLASS II	0	Follow Up 2
27	R	CLASS II	CLASS II	2	Baseline

Class I = No limitation of physical activity, Class II = Slight limitation of physical activity, Class III = Marked limitation of physical activity, and Class IV = Inability to carry out any physical activity.

SAFETY AND EFFICACY OF RT234 VARDENAFIL INHALATION POWDER ON EXERCISE PARAMETERS IN PULMONARY ARTERIAL HYPERTENSION: PHASE 2 DOSE-ESCALATION STUDY DESIGN

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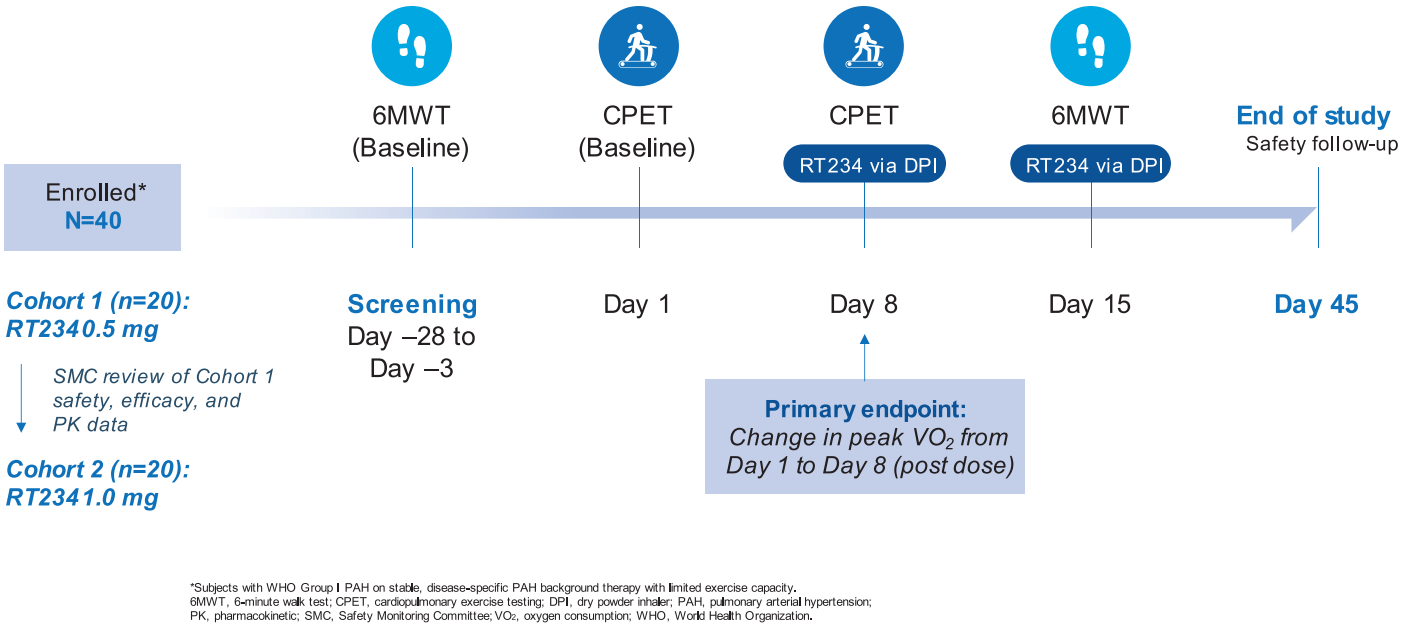
Selected Areas: Therapeutic Strategies

Background: Pulmonary arterial hypertension (PAH) is currently managed using chronic, scheduled treatments to improve exercise capacity and delay clinical worsening. Availability of an as-needed (PRN) treatment may further enhance patient quality of life by rapidly resolving symptoms associated with physical activity. RT234 is a drug and device combination of vardenafil hydrochloride and the novel axial oscillating sphere dry powder inhaler that is suitable for PRN use and has the potential to improve exercise capacity, physical activity, and associated symptoms (ie, dyspnea).
Methods: The CL202 study (NCT04266197; Sept 2020-Dec 2023 [expected completion]) is a multicenter, open-label, dose-escalation, phase 2b study designed to evaluate the safety and efficacy of RT234 on exercise parameters assessed by cardiopulmonary exercise testing (CPET) and 6-minute walk distance (6MWD) in patients with PAH (Figure).
Results: Up to 40 adult patients with right heart catheterization—confirmed World Health Organization Group 1 PAH on stable oral PAH-specific (=2) and/or inhaled



*Subjects with WHO Group I PAH on stable, disease-specific PAH background therapy with limited exercise capacity.
6MWT, 6-minute walk test; CPET, cardiopulmonary exercise testing; DPI, dry powder inhaler; PAH, pulmonary arterial hypertension; PK, pharmacokinetic; SMC, Safety Monitoring Committee; VO_2, oxygen consumption; WHO, World Health Organization.

Figure 1: CL202 study design.

therapy are being enrolled in 2 successive dose cohorts (0.5 mg; 1.0 mg). A safety monitoring committee will decide whether to proceed with the 1.0 mg cohort or terminate the study. Safety measures include adverse events (at each of 2 single-dose treatment days and for 30-day follow-up) and acute physical and cardiac effects. Efficacy measures include changes in peak oxygen capacity (Vo_2; primary endpoint) and exertional symptoms from baseline (day 1) to 15 minutes postdose during CPET on day 8, and change in 6MWD from baseline (screening, day –28 to day –3) to 15 minutes postdose on day 15.

Conclusions: Exploratory endpoints include pharmacokinetics and exposure-response analyses. The results of the CL202 study are expected to inform the design of phase 3 trials of RT234.

THYROID STORM FROM GRAVES' DISEASE ASSOCIATED WITH SEVERE PULMONARY HYPERTENSION AFTER PULMONARY THROMBOENDARTERECTOMY FOR CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

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Category: Case Report
Selected Areas: Diseases and Conditions Associated with PH

Background: While pulmonary hypertension (PH) is often cured in chronic thromboembolic PH (CTEPH) after pulmonary thromboendarterectomy (PTE), there is a risk of recurrent PH after PTE in a minority of patients.
Methods: (Case) A 50-year-old female with hypertension and hysterectomy for fibroids presented with dyspnea, severe PH and right ventricular (RV) dysfunction. Ventilation-perfusion scan (Figure 1), computed tomography angiography (CTA), and pulmonary angiography (Figure 2) revealed multiple areas of severe thromboembolic disease. She underwent urgent PTE (Figure 3) with markedly improved hemodynamics, albeit warranting resumption of sildenafil early postop. Six months postop, she developed worsening dyspnea and was restarted on 3-drug PH therapy. One year postop she had severe PH

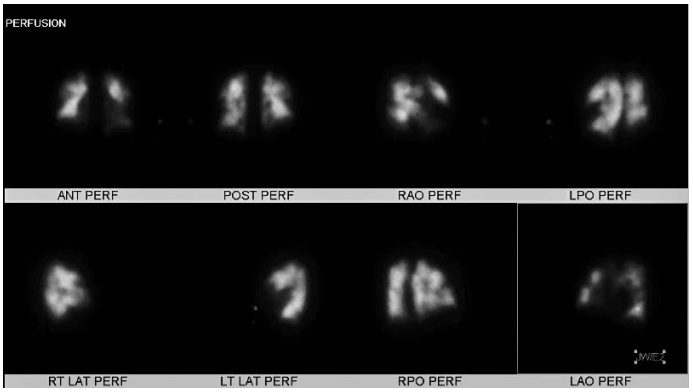

Figure 1: Preoperative perfusion scan demonstrating multiple unmatched perfusion defects in the right upper, right lower, left upper, and left lower lobes. ANT, anterior; LAO, left anterior oblique; LAT, lateral; LPO, left posterior oblique; LT, left; PERF, perfusion; POST, posterior; RAO, right anterior oblique; RPO, right posterior oblique; RT, right.

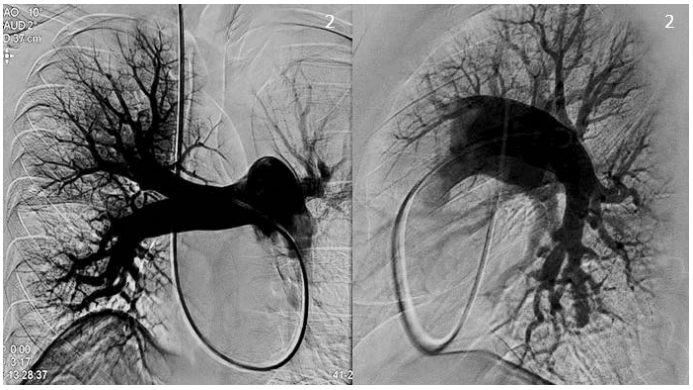

Figure 2: Preoperative pulmonary angiogram. (**Left**) Anterior-posterior view of selective right main pulmonary angiogram and (**Right**) lateral view of selective left main pulmonary angiogram showing obstructive lesions in multiple, bilateral lobar, and segmental branches.

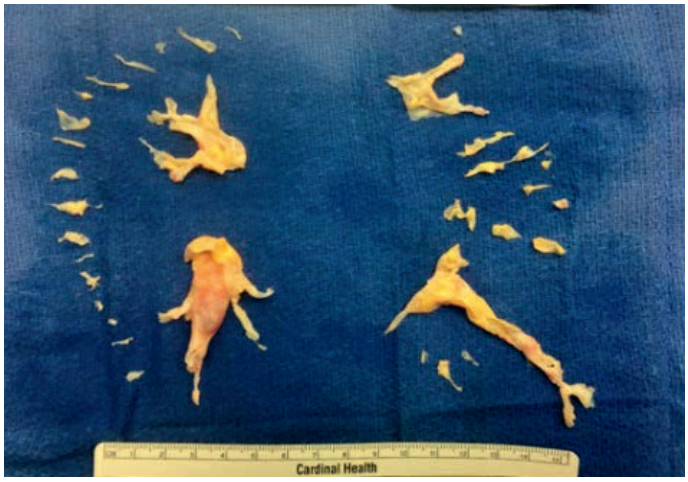

Figure 3: Clot specimen removed from pulmonary thromboendarterectomy.

despite high-dose combination PH therapy and underwent balloon pulmonary angioplasty (BPA). Ongoing fatigue and dyspnea prompted readmission 1 month later.

Results: (Decision making) Severe PH post-PTE and post-BPA should prompt consideration of PH etiologies beyond thromboembolic disease. She was noted to have persistent sinus tachycardia, bounding arterial pulses, hyperreflexia, and hyperdynamic findings on echo-Doppler (Figure 4). Thyroid studies revealed severe thyrotoxicosis leading to a diagnosis of Graves' disease. She was treated with methimazole, iodine, and steroids followed by thyroidectomy with substantial improvement in symptoms and improved RV function by echo.

Conclusions: While PH after PTE is generally related to thromboembolic disease, it may not always be. Clinical assessment of PH after PTE should include careful consideration and evaluation for thyroid disease and the broad range of medical conditions known to be associated with PH.

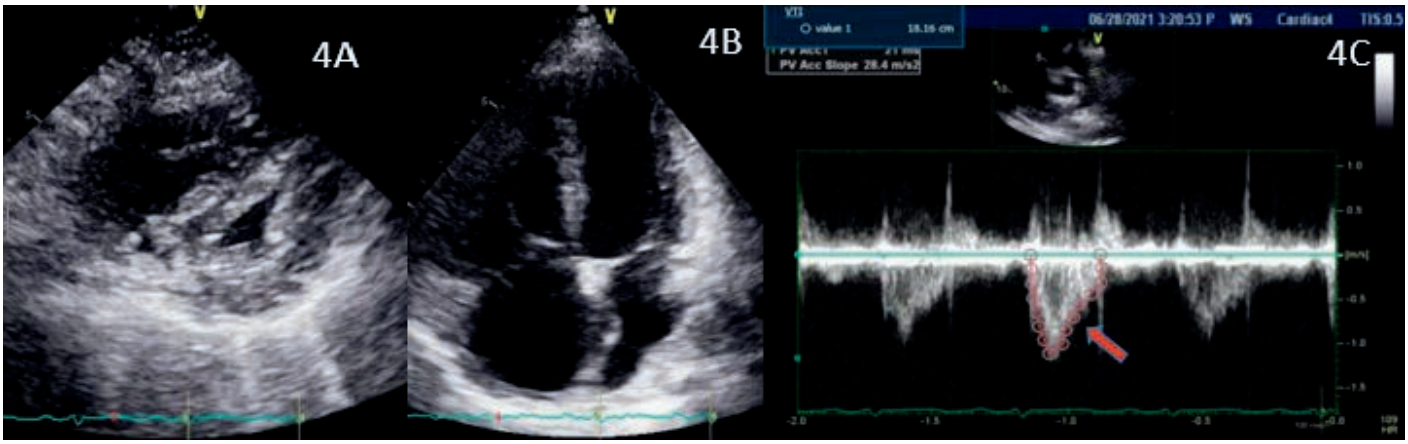

Figure 4: (**A**) Hyperdynamic LV and systolic interventricular septal flattening. (**B**) RV enlargement and dysfunction, RA dilatation and right-to-left interatrial septal bowing. (**C**) PW Doppler of the RVOT. Short acceleration time and late systolic notching (red arrow). LV, left ventricular; PW, pulsed-wave; RA, right atrial; RV, right ventricular; RVOT, RV outflow tract

ACUTE HEMODYNAMIC IMPROVEMENT IN CHRONIC PULMONARY ARTERIAL HYPERTENSION ON DUAL THERAPY FOLLOWING RT234 INHALATION

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Category: Clinical Science
Selected Areas: Quality of Life, Therapeutic Strategies

Background: RT234 is an inhaled formulation of phosphodiesterase type-5 inhibitor (PDE5i) vardenafil, in development for episodic symptoms of pulmonary arterial hypertension (PAH). This phase 2a escalating-dose trial evaluated acute changes in pulmonary vascular resistance (PVR) and other hemodynamic (HD) parameters in PAH patients on stable maintenance dual therapy.
Methods: Three cohorts received RT234 0.2, 0.6, or 1.2 mg during right heart catheterization.
Results: Of 14 subjects, age was 54 ± 14 years (79% female) and functional class was 2 (57%), 3 (36%), or 4 (7%). In the 0.2, 0.6, and 1.2 mg cohorts, respectively, mean PVR was 635 ± 344, 469 ± 431, and 579 ± 337 dyn·s/cm^5 at baseline and decreased by −6.6% (−22.2 to 2.7), 23.7% (−44.7 to −18.6), and −16.0% (−22.7 to −10.5) postinhalation. With 0.6 and 1.2 mg, PVR fell >10% at 5 minutes, a reduction sustained for 60 minutes. PVR/systemic vascular resistance ratio changed by −8.0% (−27.1 to 14.1), −18.4% (−37.8 to 0.9), and −11.9% (−23.9 to −0.3) for the 0.2, 0.6, and 1.2 mg doses, indicating the 0.6 mg dose may offer the greatest pulmonary selectivity. No clinically significant changes in systemic blood pressure or heart rate were observed. Change in PaO_2 was +1.8% (−13.5 to 27.4), +8.1% (−13.5 to 22.6), and +4.3% (−1.4 to 9.9) for the 3 doses. Improvements in pulmonary HD with 0.6 mg RT234 were on par with 20 mg oral vardenafil, with less systemic hypotension and higher oxygenation. The only treatment-related adverse events (AEs) were mild headache and mild throat irritation, each in a single subject. No respiratory AEs occurred. RT234 produced rapid reduction in PVR, sustained for 60 minutes, and was well tolerated (Figure).
Conclusions: The optimally effective RT234 dose appears to be 0.6 mg. RT234 is suited for as-needed or preemptive PAH therapy.

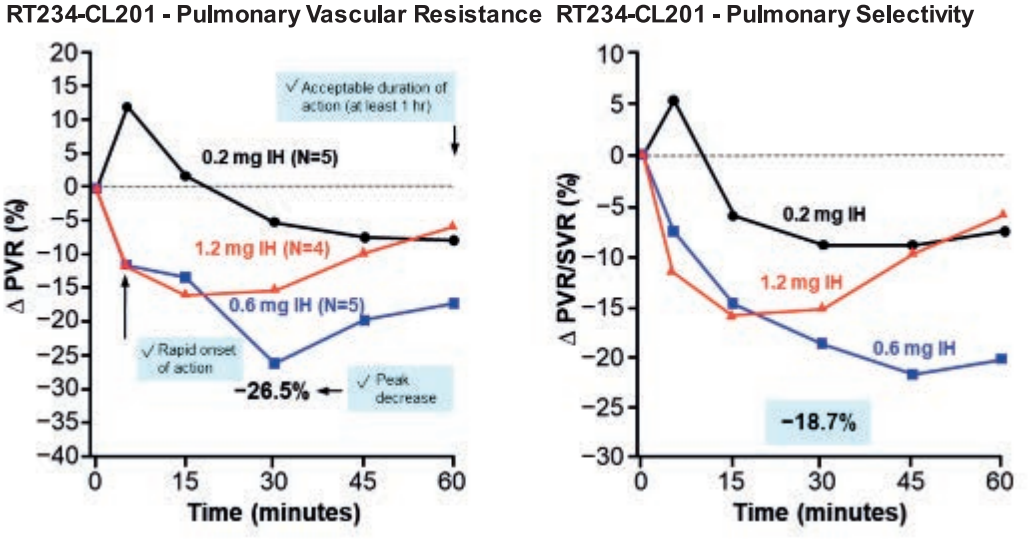

Figure 1: Hemodynamic outcomes: pulmonary vascular resistance and pulmonary selectivity up to 60 minutes post-RT234 dose.

SOCIAL DETERMINANTS OF HEALTH IN PULMONARY ARTERIAL HYPERTENSION: A CLINICIANS' PERSPECTIVE

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Category: Clinical Science
Selected Areas: Diseases and Conditions Associated with PH, Effect of COVID and Telemedicine on PH Management, Quality of Life

Background: Social determinants of health (SDOH) can affect the vulnerable pulmonary arterial hypertension (PAH) population, especially during the COVID-19 pandemic. Providers' understanding of SDOH at the point of care and their potential effect is unknown.

Methods: Semistructured virtual interviews of US health care providers (HCP) at pulmonary hypertension (PH) centers and an association were conducted (January and February 2022). A trained interviewer sought participants' perspectives of SDOH in PAH and its effect. Transcripts were developed and analyzed for key themes to assess potential policy implications.

Results: Participants served a large PAH population (Tables 1 and 2) and demonstrated high awareness of SDOH and its effect on treatment and outcomes. Patients' socioeconomic status, health insurance, education, health literacy, employment, housing, food security, transportation, and family support were reported to affect health and well-being. Further complicated by COVID-19-related social isolation, mental health and substance abuse were cited as contributing to significant inequities in care provision and outcomes. While telemedicine helped HCPs manage patients remotely during the pandemic, there was a concern for patients with limited access to this medium. Participants reported not formally screening for SDOH. With the recognition and the desire to act upon health inequities afforded by SDOH, HCPs felt that it was

Table 1. Participant and Pulmonary Hypertension Practice Characteristics[a]

Participant characteristics	(N=18)
Specialty n, (%)	
Pulmonologist	13 (72%)
Cardiologist	4 (22%)
Patient Advocate	1 (6%)
Experience treating PH-PAH population (years)	(n=17)
Average	19.3 years
Total	328 years
Range	6-37 years
Geographic Location n, (%)	
Northeast	8 (44%)
Southeast	1 (66%)
Northcentral	1 (66%)
Southcentral	2 (11%)
West	6 (33%)
PH Practice Characteristics [a]	(n=17)
Practice Setting n, (%)	
PHA Accredited PHCC	15 (83%)
Non-Accredited PHC	2 (11%)
PH Association	1 (6%)
PH Treating, Care and Research Professional Staff (n, range)	
Physicians	4 (2-9)
Nurses	2.3 (0-6)
Others	2 (0-4)
Quality of Life Assessment Tool Use n, (%)	
Yes	5 (29%)
No	12 (71%)
Risk Assessment Tool Use n, (%)	
Yes	16 (94%)
No	1(6%)
PHAR Participation n, (%)	
Yes	11 (65%)
No	6 (35%)
PHAR Patients Enrolled in Participating Sites	
Average	67
Range	2-300
Total	740

[a] Estimates based on study participant awareness and experience; PH=Pulmonary Hypertension; PAH= Pulmonary Arterial Hypertension; PHCC=Pulmonary Hypertension Care Center; PHC=Pulmonary Hypertension Center; PHAR=Pulmonary Hypertension Association Registry

Table 2. Pulmonary Arterial Hypertension Patient Population Characteristics Across Centers (n = 17)[b]

Number of patients	
Average	321
Total	5470
Range	125-600
Average Age (years, range)	52 (35-65)
Gender (%)	
Female	73%
Male	27%
Race (%)	
Caucasian	61%
African American	22%
Hispanic	12%
Asian	5%
Employment Status (%)	
Employed	43%
Unemployed	34%
Retired	23%
Health Insurance Status (%)	
Public	51%
Private	42%
Uninsured	7%
PAH Type (%)	
Idiopathic	39%
Associated	45%
Drug & toxin	11%
Heritable	5%
WHO Functional Class (%)	
FCI	7%
FCII	45%
FCIII	40%
FCIV	8%
PAH Therapy (%)	
Monotherapy	11%
Double therapy	52%
Triple therapy	37%
Average Time to Diagnosis (years)	1.5 years

[b] Estimated based on study participant awareness and experiences; PAH=Pulmonary Arterial Hypertension; WHO=World Health Organization; FC =Functional Class

vital for their centers to have a dedicated PH social worker and support staff to optimize care and outcomes.
Conclusions: Participants were highly aware of the importance of SDOH in PAH patients. An approach that integrates SDOH in care management, streamlined through institutional policy, could minimize disparities contributing to improved health care access, outcomes, and quality of care.

SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF TREPROSTINIL PALMITIL INHALATION POWDER: A PHASE 1 RANDOMIZED, DOUBLE-BLIND, SINGLE-DOSE, AND MULTIPLE-DOSE STUDY

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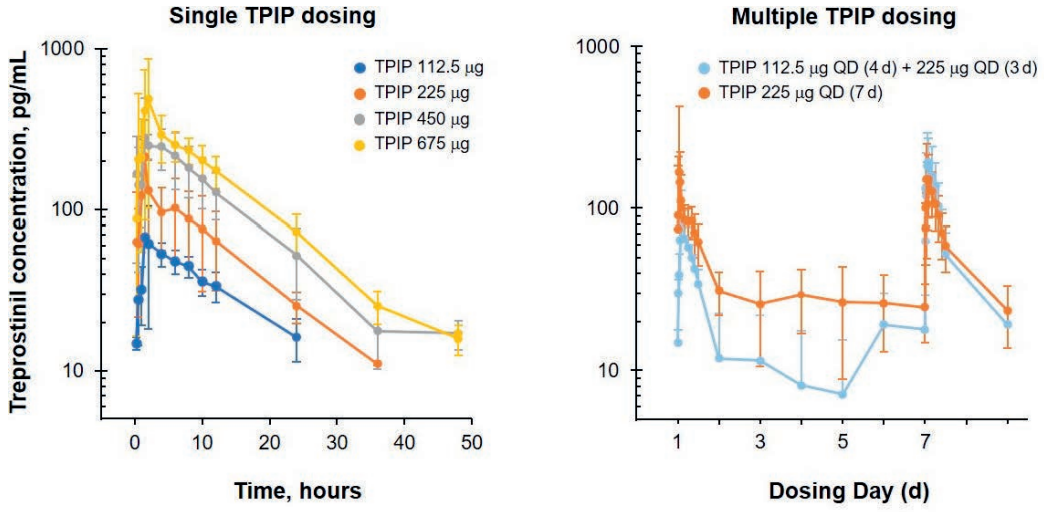
Category: Clinical Science
Selected Areas: Therapeutic Strategies

Background: Use of treprostinil (TRE) in pulmonary arterial hypertension (PAH) is limited by a short half-life ($t_{1/2}$) and dose-limiting treatment emergent adverse events (TEAEs). Treprostinil palmitil inhalation powder (TPIP) is a dry powder formulation of a TRE prodrug.
Rationale: To examine the safety, tolerability, and pharmacokinetics (PK) of single- and repeat-dose administration of once-daily (QD) TPIP.
Methods: Healthy adults received single doses of 112.5, 225, 450, or 675 mg (n = 6/dose) or placebo (n = 2) or multiple doses of 225 mg QD × 7 days (n = 6) or 112.5 mg QD × 4 days, then 225 mg QD × 3 days (n = 6), or placebo × 7 days (n = 4).
Results: Forty-one of 42 participants completed the study. Of single-dose participants, 70.8% (n = 17/24) experienced a TEAE versus 0% of placebo (0/2); cough (42.3%), dizziness (26.9%), throat irritation (19.2%), nausea (15.4%), and hypotension (15.4%) were most common. Of multiple-dose participants. 83.3% (n = 10/12) had a TEAE versus 50.0% of placebo (2/4); cough (58.3% TPIP versus 50.0% PLA), headache (50.0% versus 0%), nausea (33.3% versus 0%), and dizziness (25.0% versus 0%) were most common. TEAEs were mild in 69.0% (29/42) and moderate in 16.7% (7/42), with no severe or serious TEAEs. Titration of TPIP had fewer TEAEs in multiple QD dosing. TRE exposure was dose proportional, and steady-state accumulation was insignificant. Elimination $t_{1/2}$ was 8.7–11.6 hours after a single dose and 6.8–8.8 hours after multiple QD dosing (Figure).
Conclusions: TPIP was generally safe and well tolerated in healthy volunteers, with a PK profile that supports QD dosing. TEAEs were dose related and attenuated with titration.



QD, once daily; TPIP, treprostinil palmitil inhalation powder.

Figure 1: Treprostinil plasma concentrations following single and multiple once-daily (QD) treprostinil palmitil inhalation powder (TPIP) dosing.

PATHOLOGY PREDIAGNOSIS: A CASE REPORT OF RARE HISTOLOGICAL FINDINGS IN EXERCISE-INDUCED PULMONARY HYPERTENSION

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Category: Case Report
Selected Areas: Diagnosis or Screening and Physiologic Studies, Diseases and Conditions Associated with PH, Therapeutic Strategies

Background: (Case) A 49-year-old man with dyspnea and concerns for graft versus host disease after receiving a hematopoietic stem cell blood transplant for acute myeloid leukemia underwent a video-assisted thoracoscopic surgery (VATs) lung biopsy and was found to have pulmonary vascular remodeling, but preop right heart catheterization (RHC) had demonstrated normal hemodynamics. A repeat RHC with supine bicycle exercise study demonstrated exercise induced pulmonary hypertension (EiPH) with a mPA-CO slope of 3.1 mm Hg/L/min (Table 1). He was treated with riociguat and followed with cardiopulmonary exercise testing (CPET) which demonstrated gradual improvements even after he decided to wean off riociguat (Table 2). Repeat echocardiogram testing demonstrated still normal estimated pulmonary artery systolic pressure 23 mm Hg once weaned off riociguat.
Results: (Discussion) EiPH is felt to demonstrate an early spectrum of pulmonary vascular disease, but without consensus on exercise methodology and/or diagnostic criteria, it can be challenging to diagnose. Data on treatment of EiPH are even more limited. Our case demonstrated a mPA-CO slope

Table 1. Right Heart Catheterization Measurements

	Pre-op Right heart Catheterization	Exercise Right Heart Catheterization	
		Resting baseline	Peak Exercise
Right atrium (mm Hg)	2	4	9
Mean PA (mm Hg)	21	25	52
PA occlusion pressure (mm Hg)	3	11	8
Transpulmonary gradient (mm Hg)	18	14	44
Fick CO/CI (L/min, L/min/m^2)	6.80/3.48	5.37/2.63	Not calculated
Thermo CO/CI (L/min, L/min/m^2)	7.50/3.84	5.77/2.83	14.40/7.06
Pulmonary vascular resistance (Wood units)	2.4-2.7	2.4-2.6	3.1

Table 2. Cardiopulmonary Exercise Tests

			Riociguat Weaning	
	Baseline	**Riociguat 2.5 mg TID**	**Riociguat 1.5 mg TID**	**Riociguat stopped**
Time from baseline (months)	N/A	11	26	31
Time from prior study (months)	N/A	11	15	5
Workload (METS)	4.3	7.5	7.8	8.5
RER	1.18	1.01	1.14	1.09
VO_{2max} (mL/kg/min)	15.2	26.1	27.2	29.9
V_E/V_{CO2} slope	45.2	34.5	32.8	22.5
V_D/V_T ratio baseline	0.21	0.25	0.27	0.15
V_D/V_T ratio exercise	0.15	0.07	0.10	0.06
FVC (L, % predicted)	3.77 L, 77%	4.32 L, 89%	4.40 L, 91%	4.77 L, 89%
FEV1 (L, % predicted)	3.00 L, 78%	3.29 L, 87%	3.30 L, 88%	3.76 L, 90%
FEV1/FVC ratio	80%	76%	75%	79%
MVV (L/min, %)	108 L/min, 71%	85 L/min, 57%	132 L/min, 89%	129 L/min, 109%

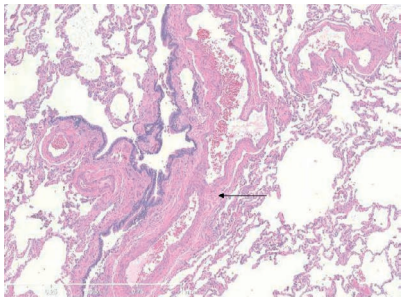

Figure 1: Hematoxylin and eosin stained histologic section of the lung showing thick wall pulmonary arteries. Note the septa (black arrow). The background lung parenchyma exhibits normal architecture, with no evidence of interstitial lung disease.

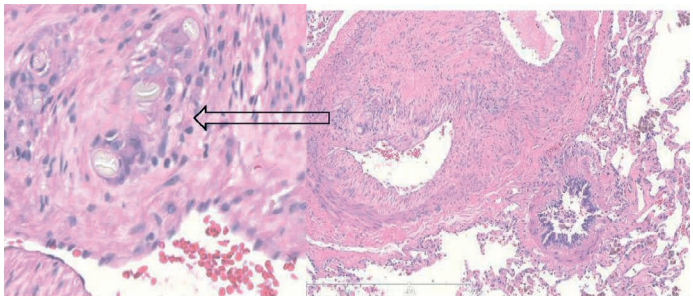

Figure 2: Hematoxylin and eosin section showing pulmonary artery with thickened wall containing basophilic nonpolarizable material and associated foreign body-type giant cell reaction (black arrow).

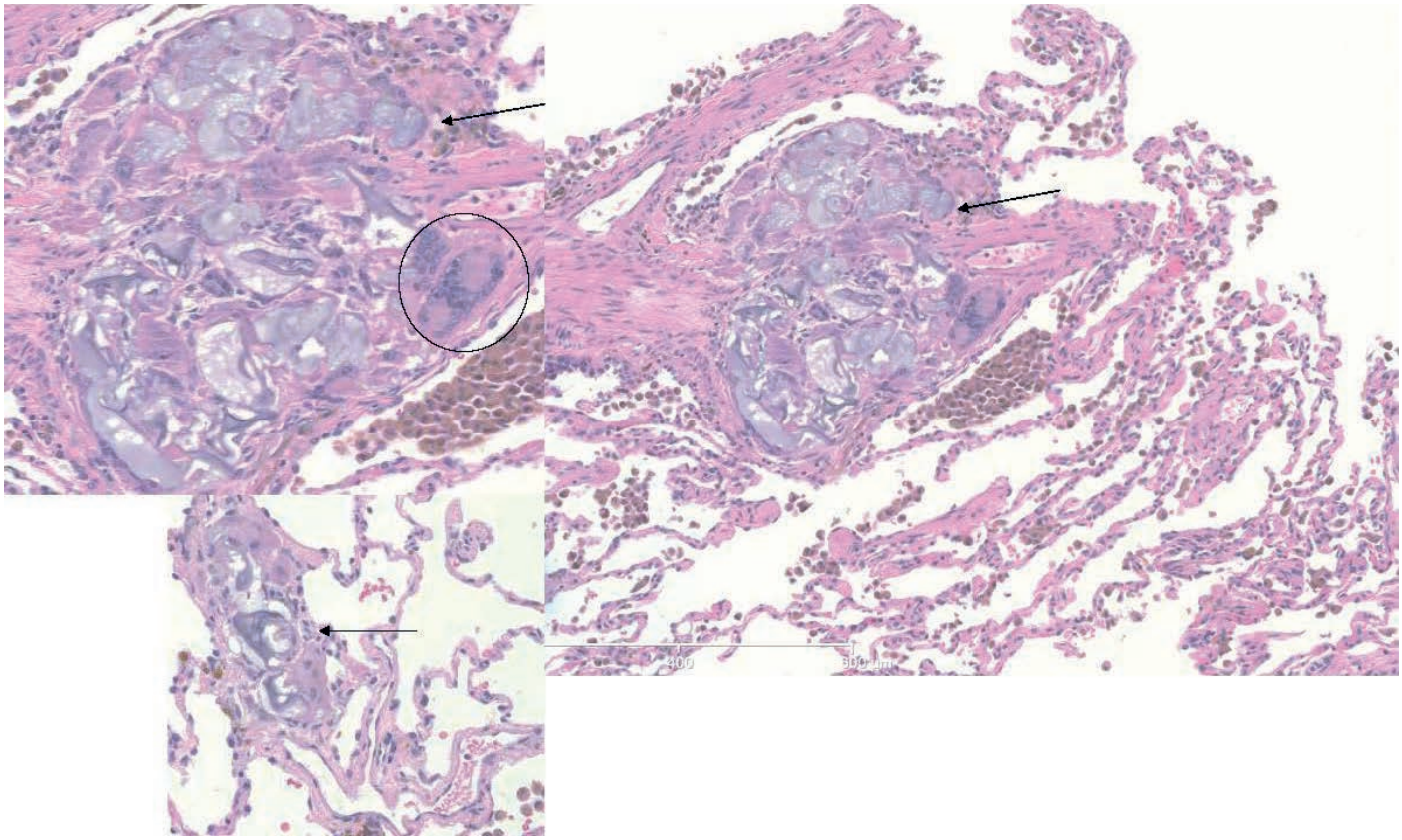

Figure 3: Hematoxylin and eosin sections showing pulmonary vessels with basophilic nonpolarizable material plugging their lumens (black arrows). This also associated with foreign body-type giant cell (circle) reaction.

> 3 mm Hg/L/min, felt to be an indicator of reduced pulmonary vascular distensibility. Furthermore, this case reinforces the importance of identifying and treating pulmonary vascular disease at its earlier disease spectrum (Figures 1–3).

Conclusions: Our case uniquely presents a histopathologic basis for EiPH demonstrating early pulmonary vascular changes on lung biopsy.

LONG-TERM EFFECTS OF ORAL TREPROSTINIL IN SUBJECTS WITH PULMONARY ARTERIAL HYPERTENSION: FREEDOM-EV OPEN-LABEL EXTENSION STUDY

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Category: Clinical Science
Selected Areas: Therapeutic Strategies

Background: Oral treprostinil (TRE) is approved to treat pulmonary arterial hypertension (PAH). FREEDOM-EV established 3 times daily (TID) TRE to delay disease progression when added to oral monotherapy. Data reported here are from subjects who transitioned to an open-label extension (OLE) study after experiencing a clinical worsening event (CWE) during the parent study or at parent study closure.

Table 1. Participant Baseline and Week 48 Characteristics, Assessments, and Reasons for Discontinuation (Observed Data Only Without Imputation)

Treatment assignment, FREEDOM-EV		Placebo (PBO)		Oral Treprostinil (TRE)	
Status at end of FREEDOM-EV		Had CWE	No CWE	Had CWE	No CWE
Baseline, N		108	150	66	144
Completed Week 48 (% baseline), N		67 (63%)	122 (81%)	46 (72%)	132 (92%)
Age at Baseline (years): Mean (SD)		49 (15)	46 (14)	48 (16)	46 (15)
Female		78%	82%	80%	78%
Dose (mg): Mean (SD)	Baseline	--	--	5.5 (3.3)	5.6 (3.4)
	Week 48	5.7 (3.8)	3.6 (2.5)	6.1 (3.6)	6.1 (3.6)
FC, Baseline	I	0 (0%)	19 (13%)	1 (2%)	21 (15%)
	II	13 (12%)	**108 (72%)**	3 (4%)	**101 (70%)**
	III	**83 (78%)**	23 (15%)	**52 (79%)**	22 (15%)
	IV	11 (10%)	0 (0%)	10 (15%)	0 (0%)
FC, Week 48	Improved	**28 (44%)**	14 (12%)	**18 (41%)**	12 (9%)
	Stable	34 (53%)	**102 (84%)**	25 (57%)	**103 (79%)**
	Worsened	2 (3%)	6 (5%)	1 (2%)	15 (12%)
FC, Change from baseline*		P<0.0001	P=0.07	P<0.0001	P=0.56
NT-pro-BNP (pg/ml): Mean (SD)	Baseline	3891 (4987)	1108 (2092)	4729 (12988)	754 (1642)
	Week 48	2262 (3318)	655 (1249)	2867 (4209)	713 (1061)
	Mean (SD) Change from baseline **	-793 (2391) P<0.03	-140 (1128) P=0.19	-86 (4083) P=0.9	-3.9 (1316.5) P=0.97
6MWD (m): Mean (SD)	Baseline	301 (116)	450 (96)	288 (138)	448 (84)
	Week 48	402 (96)	460 (91)	382 (83)	446 (91)
	Mean (SD) Change from baseline **	85 (100) P<0.0001	6 (54) P=0.19	56 (117) P<0.006	-7 (52) P=0.85
Key Reasons for Discontinuation before Closure, N (%)	Death	29 (27%)	14 (9%)	21 (32%)	4 (3%)
	Progressive disease	12 (11%)	0 (0%)	8 (12%)	0 (0%)
	Adverse event	23 (22%)	17 (11%)	8 (12%)	17 (11%)

*** p-values are calculated from McNemar's test; ** p-values are calculated from paired t-test**

Methods: Subjects attended visits at baseline (start of OLE) and every 12 weeks until voluntary discontinuation or study closure. Efficacy measures included 6-minute walk distance (6MWD), World Health Organization Functional Class (FC), and plasma NT-pro-BNP level (week 48 only).
Results: Of 690 FREEDOM-EV subjects, 470 enrolled in the OLE: 258 previously assigned placebo (PBO) and 212 assigned TRE. Baseline characteristics, dosing, and key data are presented in the Table. Mean 6MWD increased significantly from baseline in subjects initially assigned PBO with a CWE in the parent study (85 ± 100 m). NT-pro-BNP decreased significantly in previous PBO subjects with CWE. FC improved in >40% of previous PBO subjects with CWE. Discontinuations from the study due to adverse events were most common in previous PBO patients with CWE (22%). No new safety signals were observed.
Conclusions: Subjects starting TRE after CWE had a significant increase in 6MWD, improved FC, and reduced NT-pro-BNP 48 weeks after starting TRE, whereas those without CWE had small improvements in all efficacy measures after initiating TRE. These data are consistent with the placebo-controlled FREEDOM-EV results and suggest that TRE was effective in a group of higher-risk PBO subjects who had just had a CWE.

PULMONARY HYPERTENSION AND CANTÚ SYNDROME

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Category: Case Report
Selected Areas: Diseases and Conditions Associated with PH; Pediatrics

Background: Cantú syndrome has been associated with pulmonary hypertension (PH), but case reports describe it as an infantile condition, often in conjunction with a patent ductus arteriosus (PDA). Here, we present the case of an adolescent with new-onset PH in the setting of Cantú diagnosis.
Methods: (Case) An adolescent male presented after unwitnessed syncopal event and 1-month history of exertional dyspnea and orthopnea. Review of symptoms was remarkable only for nausea, emesis, fatigue, dry nighttime cough, and bilateral leg swelling for a few weeks. Of note, mother's pregnancy was complicated by polyhydramnios requiring multiple amniocenteses and delivery at 36 weeks due to macrosomia. He had a 2-week neonatal intensive care unit admission for respiratory distress and underwent surgical closure of large PDA at 6 weeks of age. His medical history included hypotonia, short stature (recently started on growth hormone), diabetes, elevated body mass index, learning disability, and attention deficit hyperactivity disorder on methylphenidate. Chest x ray showed significant cardiomegaly and chest computed tomography scan had dilation of the pulmonary arteries. Echocardiogram revealed a large pericardial effusion with severe PH. Initial brain natriuretic peptide (BNP) level was elevated to 168 pg/mL. He was tachycardic, mildly hypertensive, and admitted to the intensive care unit for further evaluation and monitoring. Cardiac catheterization revealed mean pulmonary artery pressure 44 mm Hg, wedge pressure 18 mm Hg, and pulmonary vascular resistance 4.3 Wood units, on 50% FiO_2 and nitric oxide (iNO). He was carefully transitioned from iNO to sildenafil therapy and started on diuretics with improvement. As part of the workup for PH, a sleep study revealed moderate obstructive sleep apnea (oAHI: 8.26/hour), which improved with auto-positive airway pressure (PAP) therapy, 5–10 cm H_2O. Genetic studies were also sent, part of our protocol for idiopathic PAH, and supported by distinct facial features. A mutation in the ABCC9 gene resulted, confirming the diagnosis of Cantú Syndrome. He has since been transitioned to tadalafil as an outpatient, and most recent echocardiogram shows improvement in right ventricular function.
Results: (Discussion) Cantú syndrome, also known as hypertrichotic osteochondrodysplasia, is an autosomal dominant genetic condition associated with a gain of function mutation in the ABCC9 or KCNJ8 gene, which encode regulatory and pore forming subunits of ATP-sensitive potassium (K-ATP) channels, respectively. The mechanism of PH development in patients with Cantú syndrome is likely multifactorial, related to obesity effects, obstructive sleep apnea, and risk for effusions. Although K-ATP channelopathy has been associated with development of PH, typically decreased potassium channel activity causing vasoconstriction is seen. In Cantú syndrome, it is the converse: Increased channel activity leads to vasodilation of smooth muscle, compensatory cardiac hypertrophy, and increased cardiac output. The association of PH and Cantú-related channel disease is therefore not clear, and further mechanistic studies are needed. To our knowledge, this is the first noninfantile Cantú syndrome patient with PH. Cantú syndrome patients are reported to develop PH during infancy, perhaps related to PDA physiology, and there is improvement with resolution of the PDA. Although our patient did have a PDA, he did not have any evidence of PH on infantile or childhood studies. Therefore, we hypothesize that PH development in our patient was secondary to the cumulative effect of several risk factors, including Cantú syndrome, obstructive sleep apnea, exposure to methylphenidate therapy, and exposure to growth hormone. This case illustrates the importance of monitoring patients with this syndrome for the development of PH as they grow older and develop other comorbidities. We also highlight the potential for stabilization and improvement of PH with phosphodiesterase inhibitors.
Conclusions: PH should be considered when a patient Cantú syndrome presents with cardiopulmonary issues regardless of age. Further studies are warranted to examine the link between the 2 conditions.

FACEMASKS AND WALK DISTANCE IN PULMONARY ARTERIAL HYPERTENSION PATIENTS

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Category: Clinical Science
Selected Areas: Diagnosis or Screening and Physiologic Studies, Effect of COVID and Telemedicine on PH Management

Background: Facemask wearing is a key control measure to prevent transmission of SARS-CoV-2. However, widespread face mask use has proven challenging. Frequently asserted reasons for noncompliance with facemask wearing include heightened breathlessness and carbon dioxide retention and/or hypoxemia, especially during exertion. Our objective was to evaluate whether facemask wearing affected distanced covered, rating of perceived exertion (RPE), and arterial oxygen saturation (SpO_2) during a 6-minute walk test (6MWT) in patients with pulmonary arterial hypertension (PAH).

Methods: Forty-five patients being treated for Group 1 PAH and who performed a 6MWT without (Test 1) and with (Test 2) a facemask between October 2019 and October 2020 (ie, be-

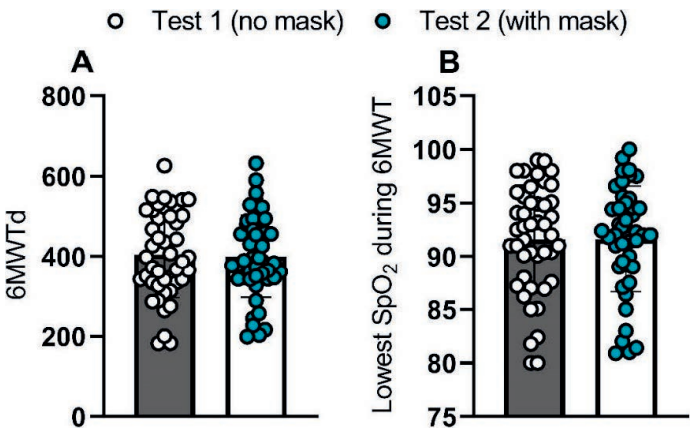

Figure 1: Group mean (solid bars) and individual patient 6-minute walk test distance (6MWTd) and lowest arterial oxygen saturation (SpO_2) during 6-minute walk tests without (Test 1, white circles) and with a facemask (Test 2, blue circles).

Table 1. Descriptive Characteristics, Clinical Data, and Submaximal Cardiopulmonary Exercise Test (CPET) Responses

Demographics				
Age, y	60 ± 11			
Sex	Male	9 (20.0%)		
	Female	36 (80.0%)		
Race	White	39 (86.7%)		
	Black	4 (8.9%)		
	Asian	2 (4.4%)		
Ethnicity	Not Hispanic	41 (91.1%)		
	Hispanic	4 (8.9%)		
BMI	26.8 ± 4.9			
PAH subgroup				
1.1; Idiopathic	18 (40.0%)			
1.2; Heritable	2 (4.4%)			
1.4.1; Connective tissue disease	24 (53.3%)			
1.4.4; Congenital heart disease	1 (2.2%)			
Clinical Data	**Test 1**		**Test 2**	***P*-value**
NYHA/WHO FC				.93
	I	4 (8.9%)	5 (11.1%)	
	II	17 (37.8%)	16 (35.6%)	
	III	24 (53.3%)	24 (53.3%)	
6MWTd, m	405 ± 108		400 ± 103	.81
6MWT SpO_2, %	92.8 ± 3.4		93.3 ± 3.3	.55
RPE, Borg CR10	2.5 ± 1.7		2.5 ± 2.1	.91
REVEAL Lite 2 score	8.2 ± 2.9		8.4 ± 2.8	.80
BNP, pg.mL	175 ± 342		188 ± 342	.86
RVSP, mmHg	55.7 ± 15.8		54.8 ± 16.0	.80
TAPSE, cm	2.0 ± 0.4		2.0 ± 0.5	.74
RV enlargement				.82
	None	14 (31.8%)	17 (37.8%)	
	Mild	18 (40.9%)	15 (33.3%)	
	Moderate	7 (15.9%)	9 (20.0%)	
	Severe	5 (11.4%)	4 (8.9%)	
RV dysfunction				.97
	None	25 (55.6%)	25 (55.6%)	
	Mild	11 (24.4%)	11 (24.4%)	
	Moderate	5 (11.1%)	6 (13.3%)	
	Severe	4 (8.9%)	4 (8.9%)	
Submaximal CPET	**Test 1**		**Test 2**	***P*-value**
Resting SpO_2, %	96 ± 3		96 ± 3	.48
$\dot{V}_E/\dot{V}CO_2$ slope	38.0 ± 9.7		38.7 ± 11.1	.74
$\Delta P_{ET}CO_2$, mmHg	2.2 ± 2.1		2.1 ± 2.0	.88

6MWTd, six-minute walk test distance; SpO_2, arterial oxygen saturation; RPE rating of perceived exertion; BNP, brain natriuretic peptide; RVSP, right ventricular systolic pressure; TAPSE, tricuspid annular plane systolic excursion; RV, right ventricle.

fore and after implementation of a facemask mandate) were included.
Results: At both time points, all patients also underwent a submaximal cardiopulmonary exercise test, echocardiogram, and blood laboratory tests, with a REVEAL Lite 2.0 score calculated (Table). The 6MWTs were performed 81 ± 51 days apart. All patients were clinically stable at both testing timepoints. 6MWT distance was not different between Test 1 versus Test 2 (405 ± 108 m versus 400 ± 103 m, $P = 0.81$; Figure). Similarly, both end-test RPE and lowest SpO_2 during the 6MWT were not different in Test 1 versus Test 2 (RPE: 2.5 ± 1.7 versus 2.5 ± 2.1, $P = 0.91$; SpO_2 nadir: 93 ± 3.4% versus 93.3 ± 3.3%, $P = 0.55$; Figure).
Conclusions: Wearing a facemask had no discernable effect on the arterial oxygen saturation and perceptual responses to exercise or exercise capacity in patients with moderate-to-severe PAH. Wearing a facemask appears to be safe in PAH patients, even during exercise.

AN INNOVATIVE APPROACH TO ENSURING SAFE MANAGEMENT OF INFUSED PROSTACYCLIN THERAPY. A QUALITY IMPROVEMENT PROJECT

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Category: Clinical Science
Selected Areas: Therapeutic Strategies

Background: Pulmonary arterial hypertension (PAH) is a rare, incurable disease that leads to right heart failure. One treatment for PAH is continuous subcutaneous (SQ) or intravenous (IV) prostacyclin infusion. These specialized therapies are potent vasodilators, some with very short half-lives, such that any interruption in the infusion can lead to serious injury or death. Direct management by a pulmonary hypertension (PH) team in the ambulatory, emergency room, inpatient, and procedural areas is essential. The purpose of this quality improvement project was to improve patient safety through creation of a best practice advisory (BPA) alert within the electronic medical record (EMR) of patients with PAH receiving an infused prostacyclin.
Methods: Using FOCUS PDCA, the PH team identified the need to ensure all health care professionals (HCPs) are alerted when a patient they encounter is receiving an infused prostacyclin. This would mitigate erroneous manipulation of the infusion by untrained HCPs and ensure the PH team is involved in clinical management, regardless of how or why the patient is seeking access to care.
Results: In collaboration with Clinical Knowledge Management and Nursing Informatics, a BPA was created (Figure). It launches upon opening the EMR of an individual with an infused prostacyclin on their active medication list. The BPA states the patient is receiving a prostacyclin infusion, interrupting the infusion could cause serious injury or death, and the PH team must be contacted. The BPA must be acknowledged by the HCP prior to proceeding into the EMR. Education was provided by the PH team to HCPs working in the Access Center, Department of Emergency Medicine, and Anesthesia.
Conclusions: The BPA has enhanced patient safety and could be explored at other PH centers.

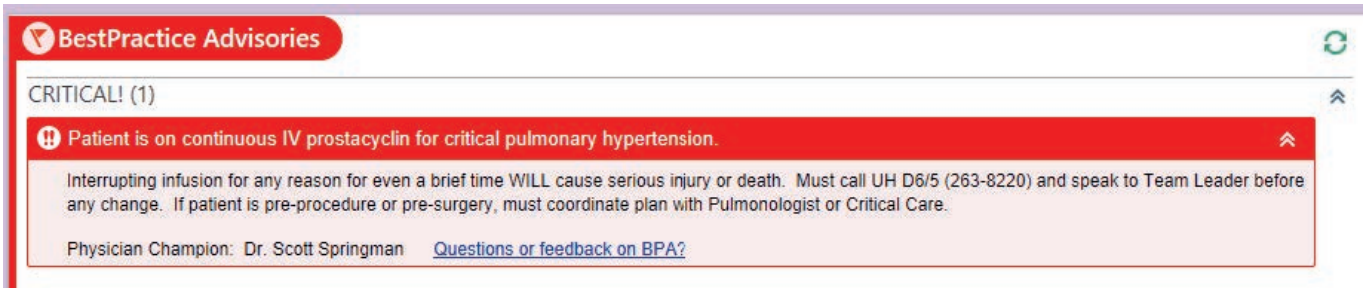

Figure 1: Screenshot of the BPA that launches upon opening the EMR of a person receiving infused prostacyclin therapy.

PULMONARY ARTERIAL HYPERTENSION RISK ASSESSMENT GENOMIC MODEL USING BAYESIAN NETWORK

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Category: Clinical Science
Selected Areas: Databases and Registries

Background: Accurate risk assessment is essential to making individualized treatment decision in pulmonary arterial hypertension (PAH) patients, yet existing probabilistic risk assessment models are insufficient since they do not include contemporary genomic and imaging biomarkers. We aimed to build a risk assessment

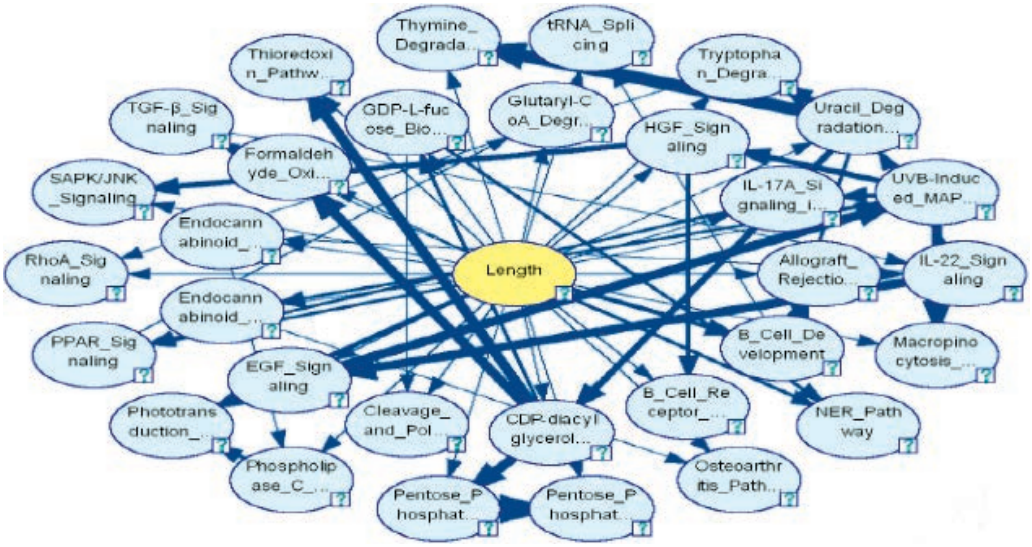

Figure 1: Genomic model Bayesian network.

PATHWAYS RED: short-term survival BLUE: long-term survival	Endothelial dysfunction	Vascular smooth muscle cell hyperplasia and proliferation	Inflammation and dysimmunity	Genetic and microenvironmental factors (DNA damage, ROS…)	Metabolism switch and/or dysfunction	RV hypertrophy / adaptation
TGF-β signaling	x	x	x		x	
SAPN/JNK signaling	x	x	x			
RhoA signaling	x	x	x	x		
PPAR signaling				x		
Phototransduction signaling			x	x		x
Phospholipase C signaling	x	x	x			
Pentose phosphate pathway		x			x	
Pentose phosphate pathway (oxidative branch)				x	x	
Osteoarthritis pathway			x			
NER pathway				x		
Macropinocytosis signaling			x			
IL-22 signaling		x		x		
UVB induced MAPK signaling				x		
Uracil degradation				x		
Tryptophan degradation		x				
tRNA splicing		x		x		
Thymine degradation				x		
Thioredoxin pathway		x		x		
GDP-L-fucose biosynthesis					x	
Formaldehyde oxidative pathway				x	x	
Endocannabinoid neuronal pathway	x	x	x			
Endocannabinoid cancer inhibition pathway						
EGF signaling		x				
Cleavage and polyadenylation of pre-mRNA				x		x
CDP-diacyl glycerol biosynthesis		x			x	
B-cell development			x			
B-cell receptor signaling			x			
Allograft rejection			x			
IL-17A signaling		x				
HGF signaling		x				x
Glutaryl-CoA degradation					x	

Figure 2: Link between each pathway and PAH natural course.

genomic model using a Bayesian network (BN) for PAH patients.
Methods: After performing a whole genome sequencing on 325 samples, variants were filtered for quality, assigned to genes, and filtered for function and population frequency. Retaining PAH patients that survived past 7 years or died prior to 5 years left 221 samples for analysis (mean age = 54 years, 50% idiopathic PAH, 81% of female). Ingenuity pathways analysis was used to generate a list of pathways containing >1 mutated gene from our dataset.
Results: Thirty-one pathways which were significantly (Fisher exact test $P < 0.05$) associated with long-term (>7 years) versus short-term (<5 years) survival were retained. Finally, a BN model, showing interdependency (arrow direction) and association weight (arrow thickness) between the 31 selected pathways and length of survival was built. The 10-fold cross-validation area under the curve averaged 0.75. Using already published peer-reviewed articles, we were able to link each of the 31 pathways to the natural history of PAH including endothelial dysfunction, vascular smooth muscular cell proliferation, inflammation and dysimmunity, genetic and environmental factors, metabolism dysfunction, and right ventricular effect (Figures 1 and 2).
Conclusions: Using a BN, we were able to provide the first PAH risk assessment genomic model including 31 pathways that may be related to the natural PAH course.

PULMONARY ARTERIAL HYPERTENSION RISK ASSESSMENT MODEL USING RANDOM FORREST AND BAYESIAN NETWORK

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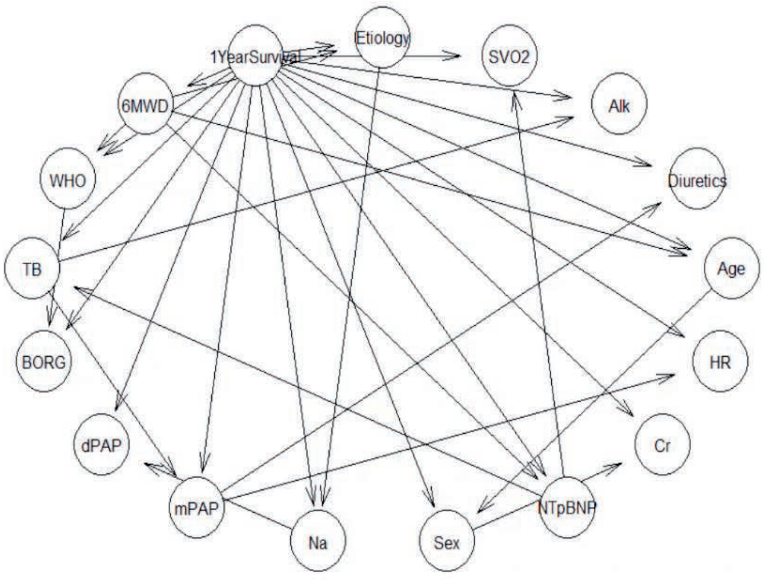
Category: Clinical Science
Selected Areas: Diseases and Conditions Associated with PH

Background: Existing risk assessment models in pulmonary arterial hypertension (PAH) are powerful in predicating survival, yet they are limited in accounting for the internal relationships among variables since they typically assume the independence between variables and their linear association with outcomes. To break free of these limits, we aimed to build a clinical risk assessment model using machine learning methods.
Methods: We harmonized clinical data measured at baseline from 7 adult PAH trials: GRIPHON, SERAPHIN, EARLY, COMPASS-2, COMPASS-3, MAESTRO, and TRANSIT-1. The harmonized data comprised 2870 subjects (mean age = 43



Variable	Thresholds
Age	Male: ≤ 65 / > 65, Female: ≤ 50 / > 50
6MWD (m)	> 440 / 440-200 / < 200
TB (mg/dl)	< 1 / 1-1.5 / > 1.5
BORG	≤ 2 / 2-5 / > 5
SVO2 (%)	> 65 / 60-65 / < 60
Na (mEq/L)	< 135 / 135-145 / > 145
dPAP (mmHg)	≤ 14 / > 14
mRAP (mmHg)	≤ 6 / 6-13 / > 13
Alk (UI/l)	≤ 150 / > 150
Cr (µmol/L)	≤110 / >110
NTpBNP (ng/l)	< 300 / 300-1400 / > 1400
HR (bpm)	≤ 90 / > 90
WHO	I, II, III, IV
Sex	Male, Female
Diuretics	Yes, No
Etiology	Collagen vascular disease, Congenital heart disease, Connective tissue disease, Drugs and toxins, HIV, Idiopathic or familiar

Figure 1: Bayesian network predicting 1-year survival using selected clinical variables.

years, 77% female, 50% idiopathic or familial PAH) and 125 clinical variables, with a mortality rate being 14%. We split the data into 80% as the training dataset and 20% as the test dataset.
Results: Using the training data, we studied variable importance in predicting time to mortality by implementing Random Forest. Sixteen variables with importance values >0.0015 were selected to construct a Bayesian network (BN; Figure) in predicting the 1-year survival status (primary outcome). The thresholds to discretize continuous variables were determined based on clinical knowledge. The BN obtained an area under the curve (AUC) of 0.85 validated using the test dataset. In 5-fold cross-validation, the average AUC was 0.77.
Conclusions: Machine learning provides new powerful methods to build PAH risk assessment models, taking the interdependence among variables into account.

EFFECTS OF FACE-TO-FACE EDUCATIONAL NURSING SUPPORT ON PATIENT COMPLIANCE WITH ORAL PULMONARY ARTERIAL HYPERTENSION THERAPIES

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Selected Areas: Databases and Registries, Therapeutic Strategies

Table 1. Baseline Characteristics

	Study (N = 107)	Control (N = 213)	p-value
Age, mean (SD)	65.1 (15.1)	55.1 (21.1)	**0.0001**
Gender male, N (%)	49 (45.8)	57 (26.8)	**0.0006**
Median income in the patient household area, mean (SD)	$52,061 ($24,577)	$52,669 ($20,285)	0.8141
College degrees in the patient household area, mean rate (SD)	15.8% (8.0%)	15.4% (7.4%)	0.6120
African-American, mean rate (SD)	18.7% (25.6%)	18.5% (24.9%)	0.2749
Asian, mean rate (SD)	2.3% (3.4%)	4.3% (9.4%)	**0.0331**

Table 2. Medication Characteristics by Group

6-month*	Study (N = 107)	Control (N = 213)	p-value
Fill Count	5.1	4.5	**0.0016**
Medication possession ratio (MPR)	86.4%	75.0%	**0.0013**
First Fill Drop Off Rate	2.7%	5.7%	0.1438

* Controlled for patients' characteristics through the regression model

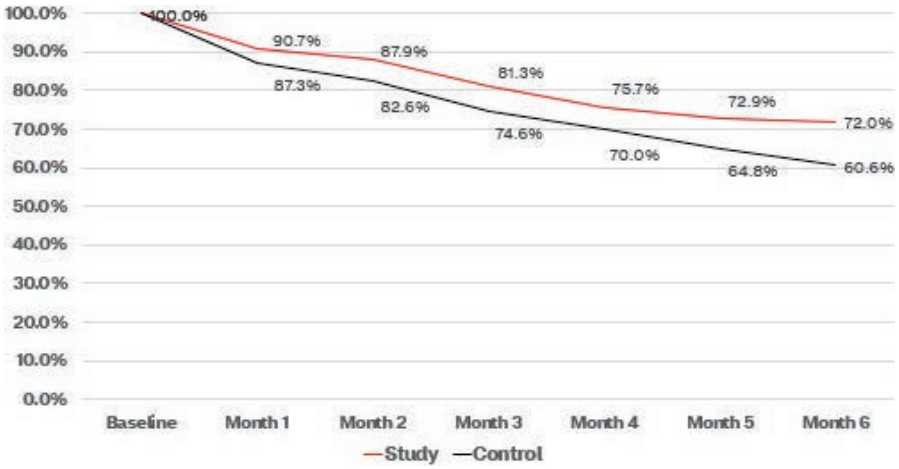

Figure 1: Persistency comparison of nurse-supported therapy versus control.

Background: Therapies currently available to treat pulmonary arterial hypertension (PAH) patients do not reverse the disease; however, they improve pulmonary hemodynamics and offer symptomatic relief and lengthen the time to clinical worsening. These therapies do not come without their challenges, which include side effects and compliance with challenging titration regimens. Health care professionals (HCPs), particularly nurses, play a significant role in improving patient medication adherence. The purpose of this study is to determine the effect that in-home, face-to-face nursing visits have on optimal adherence to oral PAH therapies.
Methods: We identified patients who received an oral PAH drug (riociguat, selexipag, or treprostinil) supported by a nursing program (study group) and patients who received an oral PAH drug (bosentan, ambrisentan, or macitentan) not supported by a nursing program (control group) using CVS Health pharmacy data from January 1, 2018, to June 30, 2019. A logistic regression model examined demographic and medication factors associated with adherence (Table 1).
Results: From January 2018 to June 2019, we identified 107 patients in the study group and 213 patients in the control group. After 6 months, patients in the study group reported 0.6 more fill counts (5.1 versus 4.5; $P < 0.01$), an 11% higher medication possession ratio (MPR; 86.4% versus 75.0%; $P < 0.01$), and higher rates of persistence (72.0% versus 60.6%; $P < 0.05$) than those in the control group. First-fill discontinuation rate was 3% higher (2.7% versus 5.7%; $P = 0.14$) in the control group and more likely to discontinue therapy in the first 6 months following the index fill (HR = 1.52; $P = 0.06$; Table 2, Figure).
Conclusions: Patients supported by nursing had significantly higher adherence.

ESTROGEN PARADOX IN METHAMPHETAMINE (MA)-ASSOCIATED PULMONARY ARTERIAL HYPERTENSION IN ANIMAL MODEL USING BINGE-CRASH MA ADMINISTRATION

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Category: Basic Science
Selected Areas: Diagnosis or Screening and Physiologic Studies

Background: Estrogen paradox describes the increased incidence of pulmonary arterial hypertension (PAH) while having better outcomes in women and female animals. There are limited data suggesting that effects of amphetamine may be modified by sex in several cardiovascular outcomes. We hypothesize the effects of methamphetamine (MA) on the pulmonary vasculature are modified by sex in the binge-crash model of MA administration.
Methods: Experimentally naïve male and female Wistar rats will be used in the study. During a 96-hour procedure of the binge-crash model of MA administration, they will be housed in experiment chamber and will be returned to temperature- and humidity-controlled animal facility for 72 hours. Rats will be trained to self-administer MA by pressing one of the response levers. At the end of the exposure period (8 weeks), the animals will be euthanized, and lungs and hearts collected for histological evaluation and right ventricular/left ventricular septum (RV/LVS) weight ratio measurements. The lungs will be inflated and fixed in formalin overnight. The left lung will be blocked and embedded in paraffin. All sections will be cut and stained with hematoxylin and eosin.
Results: Preliminary data showed that MA-exposed male rats had more inflammation—demonstrated by congestion—than control female and MA-exposed female rats. The arteriolar wall was found to be thinner in MA-exposed female rats than control female rats and MA-exposed male rats (Figure)
Conclusions: Preliminary data demonstrated congestion and arteriolar wall changes in MA-exposed rats, more prominent in male rats. This may suggest estrogen paradox phenomenon in MA-PAH from the binge-crash model.

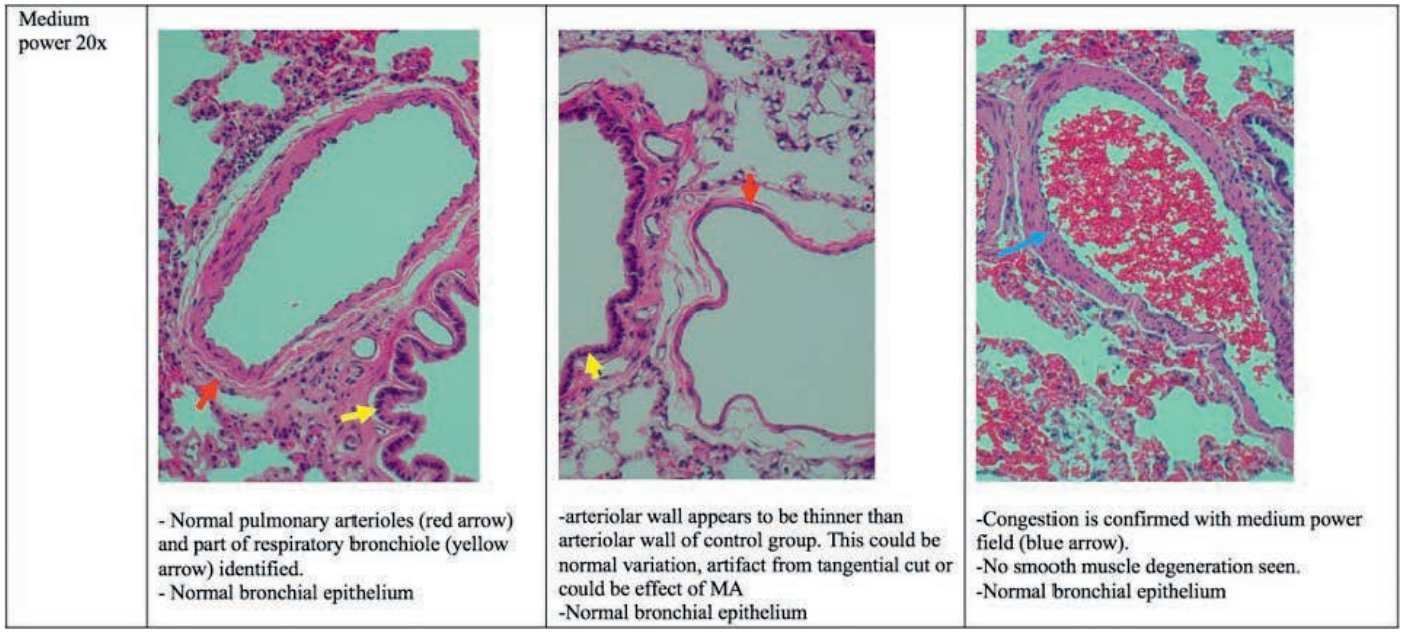

Figure 1: Ateriolar wall changes and congestion in methamphetamine (MA)-exposed rats.

LUNG TRANSPLANT OUTCOMES IN PATIENTS WITH PULMONARY VENO-OCCLUSIVE DISEASE

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Category: Clinical Science
Selected Areas: Databases and Registries, Diseases and Conditions Associated with PH

Background: Pulmonary veno-occlusive disease (PVOD) is a rare cause of pulmonary hypertension. Most patients need lung transplantation (LTx) as a curative treatment. Previous authors showed that PVOD patients had higher waitlist mortality than pulmonary arterial hypertension (PAH) patients. However, there are no reports on outcomes of LTx in this population. We would like to compare LTx outcomes between PVOD and idiopathic PAH (IPAH) patients.

Methods: This is a retrospective observational study. Patients with a diagnosis of PVOD and PAH underwent LTx between 2005 and 2018 were identified from SRTR database. Numerical data were reported in mean ± SD. Categorical data were reported in count and percent. *T*-tests and χ^2 tests were performed to compare variables between 2 groups. Survival was compared using the Kaplan-Meier (K-M) method.
Results: Sixty-one PVOD patients and 970 PAH patients who underwent LTx were identified. Patients with PVOD had significant lower posttransplant systolic, diastolic, and mean pulmonary artery (PA) pressure and higher cardiac output. Lung allocation score (LAS) at matching were not significantly different. PVOD patients had shorter time on the waiting list (152.7 versus 337.6, $P < 0.01$). The proportion of patients requiring extracorporeal membrane oxygenator (ECMO) post-LTx were higher in the PVOD group (13.11% versus 4.23%, $P < 0.01$). The proportion of patients developing primary graft dysfunction (PGD) was lower in the PVOD group (37.5% versus 61.93%, $P = 0.056$). There was no difference of length of stay, FEV1, FVC, PCO_2 post-LTx, or acute rejection. Survivals were not different using the K-M method ($P = 0.33$; Figure).
Conclusions: PVOD patients had shorter waiting time than PAH patients, suggestive of higher disease severity in PVOD than IPAH. Though more PVOD patients required ECMO support postoperative, long-term outcomes were not different.

	IPAH(970)	PVOD(61)	p-value
Recipient age (year)	39.84±16.27	39.87±21.55	0.99
Gender (F)	654(67.42%)	35(57.38%)	0.11
BMI	24.04±5.06	24.35±5.1	0.64
Post Ltx PASP (mmHg)	88.63±22.79	71.14±22.58	<0.01
Post Ltx PADP (mmHg)	40.01±13.7	34.76±13.49	<0.01
Post Ltx mPAP (mmHg)	57.5±16.36	47.38±16.65	<0.01
Post Ltx PCWP (mmHg)	12.69±7.6	11.39±7.67	0.24
Post Ltx Cardiac output	4.3±1.54	4.79±2.03	0.03
Previous cigarette smoking	186(38.11%)	29(47.54%)	0.16
LAS at matching	45.82±14.28	47.04±14.79	0.53
Time on wait list (days)	337.56±511.14	152.7±263.34	<0.01
Ischemic time (hours)	5.18±1.51	5.69±1.91	0.01
On ECMO after lung transplant	41(4.23%)	8(13.11%)	<0.01
Acute rejection	62/528(11.74%)	10/61(16.39%)	0.29
Post Ltx HD	141/896(15.74%)	7/61(11.48%)	0.37
reintubated	160/519(30.83%)	20/61(32.79%)	0.75
PGD	109/176(61.93%)	6/16(37.5%)	0.056
Length of stay	35.71±41.35	33.38±33.40	0.67
FEV1 post Ltx (%predicted)	68.49±19.78	70.9±17.31	0.39
FVC post Ltx (%predicted)	75.53±18.84	79.1±18.93	0.19
PCO2 post Ltx (%predicted)	35.79±9.77	36.04±9.14	0.86

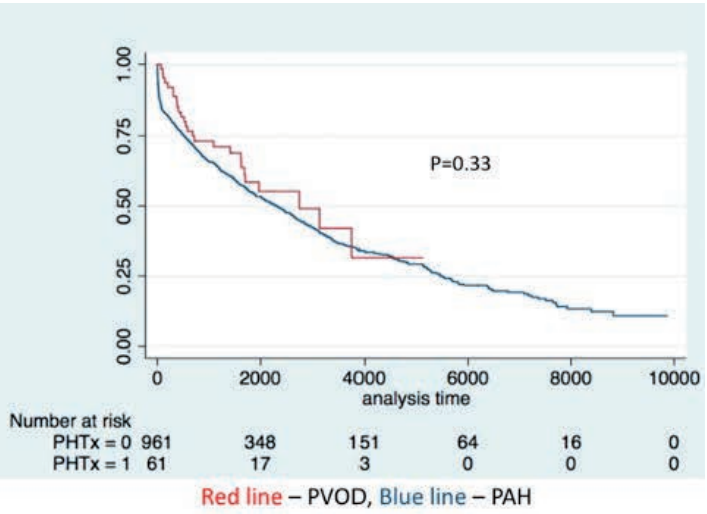

Figure 1: (**Left**) Patient data and (**Right**) Kaplan-Meier survival estimates.

AN UNUSUAL CASE OF CEREBRAL EMBOLISM AFTER INITIATION OF SELEXIPAG FOR SARCOIDOSIS-RELATED PULMONARY HYPERTENSION

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Category: Case Report
Selected Areas: Diseases and Conditions Associated with PH

Background: Pulmonary hypertension is a rare complication of sarcoidosis. Herein, we present the case of a 63-year-old female with a diagnosis of ocular and cutaneous sarcoidosis who developed shortness of breath and was referred to our department to rule out cardiac sarcoidosis.
Methods: Swan-Ganz catheterization was performed, and she was diagnosed with pulmonary arterial hypertension and started on selexipag.
Results: A few days after starting treatment, she presented with hemiplegia and was diagnosed with cardiogenic cerebral embolism by magnetic resonance imaging. As there was no evidence of preexisting intracardiac thrombosis, we suspected unusual cerebral embolism. Echocardiography revealed a deep venous thrombus (DVT), and a bubble study showed a right-left shunt through a patent foramen ovale (PFO) (Figures 1–4).
Conclusions: Based on the above, we concluded that the initiation of selexipag improved pulmonary blood flow and caused unusual cerebral embolism. This report highlights the importance of confirming PFO and DVT before starting treatment for pulmonary hypertension.

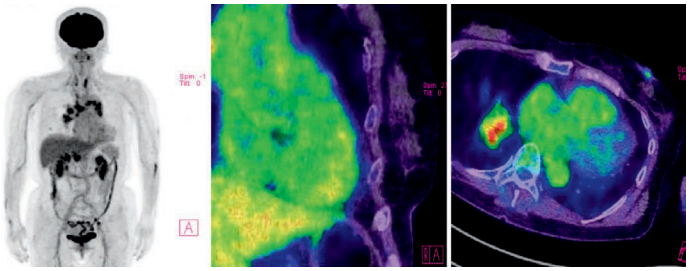

Figure 1: 18F-fluorodeoxyglucose-positron emission tomography/computed tomography scan showed accumulation in enlarged lymph nodes (red nodule) in the hilar region of the longitudinal lung, but no abnormal accumulation in the myocardium.

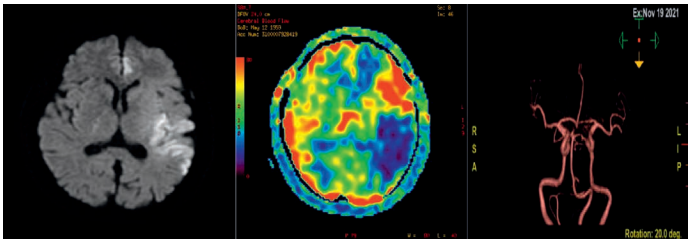

Figure 2: A head magnetic resonance imaging (MRI) scan showed acute infarction in the left frontal and parietal lobes.

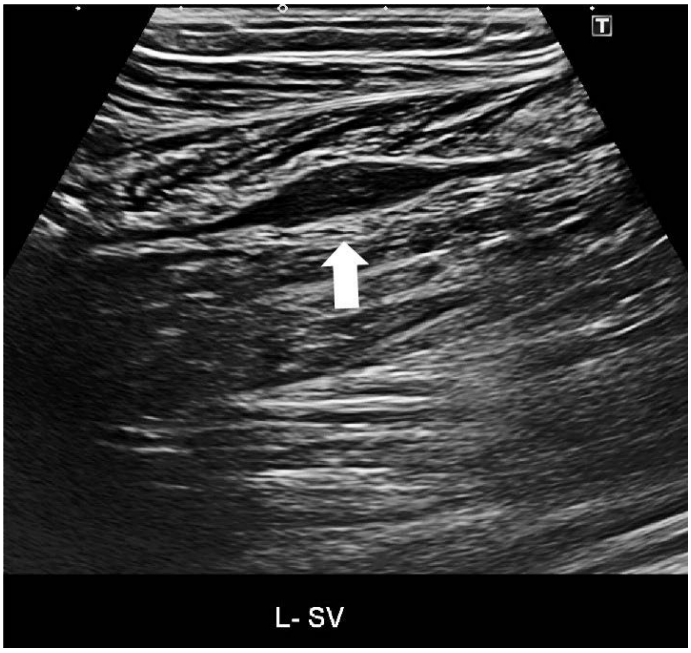

Figure 3: Echocardiography of the lower extremities showed thrombus formation (white arrow) mainly in the left soleus vein.

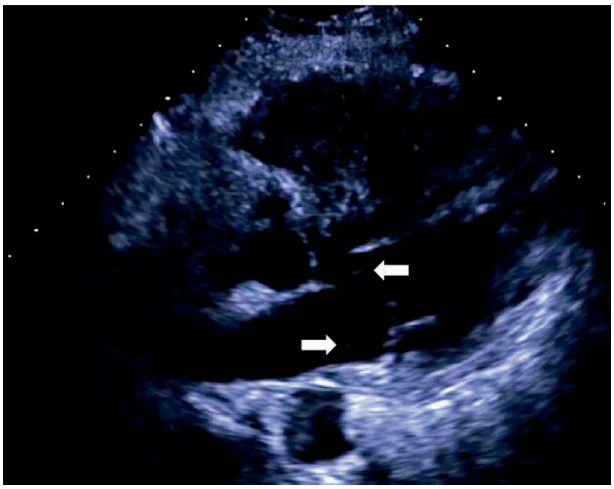

Figure 4: The microbubble (white arrows) test showed a right-left shunt that may have been mediated by the opening of the foramen ovale.

RKER-012, A NOVEL ACTIVIN RECEPTOR TYPE IIB LIGAND TRAP, REDUCED CARDIAC AND PULMONARY PATHOLOGY IN A SUGEN-HYPOXIA MODEL OF PULMONARY ARTERIAL HYPERTENSION

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Category: Basic Science
Selected Areas: Therapeutic Strategies

Background: Pulmonary arterial hypertension (PAH) is characterized by elevated pulmonary vascular resistance resulting in impaired cardiac output and right ventricle (RV) overload. PAH is associated with imbalanced TGF-β signaling, including insufficient activation of SMAD1/5/9. In preclinical studies and clinical trials, rebalancing SMAD signaling with an activin receptor type IIB (ActRIIA) ligand trap has shown benefit but can also increase red blood cells (RBCs), a potentially dose-limiting effect for PAH. KER-012 is an investigational modified ActRIIB ligand trap designed to target ActRII signaling to favor SMAD1/5/9, potentially rebalancing signaling without affecting RBCs.
Methods: We evaluated a research form of KER-012 (RKER-012) to prevent pulmonary and RV dysfunction in a sugen-hypoxia (SH) rat model of PAH. On day 1, 2 groups of Sprague Dawley rats received a single subcutaneous (SQ) dose of SUGEN5416 and were placed in a hypoxic environment (10%–12% O_2). For 3 weeks, SH rats received either vehicle (VEH) or 10 mg/kg RKER-012 twice weekly SQ. A third group serving as healthy controls received VEH twice weekly and remained in a normoxic (NX) environment.
Results: Relative to NX rats, VEH-treated SH rats (VEH-SH) had significantly increased systolic pulmonary arterial pressure (sPAP) and Fulton index (FI; ps < 0.0001), and a trend for increased RBCs ($P = 0.06$), potentially a compensatory response to hypoxia. Relative to VEH-SH, RKER-012 treatment significantly reduced sPAP (–44.5%) and FI (–28.0%; ps < 0.001), with no observed additional change in RBCs.
Conclusions: These results demonstrate that RKER-012 prevented pulmonary and RV dysfunction without affecting RBCs in a rat PAH model. We believe these results provide early evidence that KER-012 has the potential to treat human PAH without a potentially dose-limiting RBC effect.

PROVIDING INNOVATIVE CARE FOR PULMONARY ARTERIAL HYPERTENSION WITHIN THE INTEGRATED HEALTH SYSTEM-OWNED SPECIALTY PHARMACY

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Category: Clinical Science
Selected Areas: Diseases and Conditions Associated with PH, Quality of Life, Therapeutic Strategies

Background: The integrated health system-owned specialty pharmacy provides an innovative approach to providing high touch service for patients living with rare disease and complex conditions. The physical presence of an in-clinic patient liaison promotes direct provider engagement, and the fully integrated patient management platform enables clinical pharmacists and nurses to follow a patient's journey across the continuum of care.
Methods: The integrated health system-owned specialty pharmacy is uniquely positioned to clinically manage rare and complex disease states, such as pulmonary arterial hypertension (PAH). Patient liaisons, clinical pharmacists, and nurses play integral roles in onboarding PAH patients and monitoring progress across their clinical journey.
Results: Using standardized, validated assessment tools such as EmPHasis-10, clinical pharmacists and nurses review patient-reported outcomes specific to PAH and assess patient quality of life. Clinicians perform an individualized risk stratification for each patient and adjust the cadence of follow-up assessments based on disease severity. For patients who report the severest of symptoms, clinicians work directly with the provider and the care team to adjust medications and address potential medication nonadherence concerns.
Conclusions: Since several of the medications used in the treatment of PAH require Food and Drug Administration Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use, the integrated pharmacy care model also encompasses manufacturer data reporting, REMS program compliance, and desktop audit support. For these medications, early results demonstrate 100% REMS audit compliance, attributed to a dedicated clinical team and full integration with the health system electronic medical record.

CLINICAL PRESENTATION AND HEMODYNAMICS OF ADULTS WITH EISENMENGER SYNDROME AND PULMONARY ARTERIAL HYPERTENSION AFTER DEFECT CLOSURE

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Category: Clinical Science
Selected Areas: Diseases and Conditions Associated with PH

Background: To assess clinical, functional, and hemodynamic characteristics of patients with pulmonary arterial hypertension (PAH) associated with congenital heart defect (CHD) and Eisenmenger syndrome (ES) in comparison with patients with PAH after defect closure.
Methods: Here, 56 patients (mean age = 39.1 ± 14.3 years, 46 women): 30 patients with PAH-CHD and ES and 26 patients with PAH after defect closure from the Russian National Registry of Patients with PAH (NCT03707561) were followed for 24 months. Clinical parameters, 6-minute walk test, echocardiogram, and right heart catheterization (RHC) were prospectively recorded.
Results: The age at the onset of symptoms in PAH-CHD and ES was 18.2 ± 15.1 years versus 32.9 ± 14.9 years in PAH after defect closure ($P = 0.003$). The mean time from the occurrence of complaints until the final diagnosis was 36 months for ES and 9 months for PAH after defect closure ($P = 0.0006$). The mean age of atrial septal defect correction was 50 years. Mean time to development of PAH was 4 years. The mean age of ventricular septal defect and patent ductus arteriosus correction was 5 years. Mean time to development of PAH was 20 years. The main complaints were dyspnea (95%) in both groups, but in the ES group, hemoptysis (13%, $P = 0.03$) and weakness (31%, $P = 0.02$) were significantly more frequent. According to echocardiogram, patients with ES had significantly greater right ventricular hypertrophy, higher mean pulmonary arterial pressure (PAP), and patients with PAH after defect closure had the lowest tricuspid annular plane systolic excursion (TAPSE) and the greatest dilatation of right atrium and vena cava inferior. According to RHC, mean PAP and pulmonary vascular resistance were significantly higher in patients with ES. The survival rate of patients with ES was better than with PAH after defect closure (80.5% and 47.9%, respectively).
Conclusions: Our data suggest that adults with ES have more favorable hemodynamic profiles which may result in better prognoses than adults with PAH after defect closure.

IMAGING FINDINGS OF CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION—A PICTORIAL ESSAY

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Category: Clinical Science
Selected Areas: Diagnosis or Screening and Physiologic Studies

Background: Chronic thromboembolic pulmonary hypertension (CTEPH) is a life-threatening complication of pulmonary embolism (PE). Delay in diagnosis and treatment is associated with poor outcomes. CTEPH is underreported due to nonspecific signs and symptoms, underuse of ventilation-perfusion (VQ) scans, and underrecognition of CTEPH signs on computed tomography pulmonary angiogram (CTPA) and computed tomography (CT).
Methods: Using our image library, we will discuss findings and provide clinical correlation for our cohort of CTEPH patients.
Results: Signs of preexisting CTEPH include findings of chronic PE (eccentric filling defect, abrupt tapering, stenosis ± poststenotic dilatation, webs or bands, calcified thrombus, and dilated bronchial arteries) on CTPA and findings related to pulmonary hypertension (right ventricular hypertrophy, right atrial dilatation, flattening of the interventricular septum, pulmonary artery dilatation, and mosaic attenuation) on CT.

If signs of CTEPH plus acute PE are visualized, acute-on-chronic events should be suspected. In situ pulmonary artery thrombosis, pulmonary artery sarcoma, tumor emboli, and pulmonary vasculitis are all CTPA CTEPH mimickers. A positive VQ scan for CTEPH differs from acute PE and includes at least 1 segmental or larger mismatched perfusion defect. As mismatched perfusion defects can be found in many other conditions altering pulmonary blood flow, further imaging correlation is necessary.

Conclusions: The presence of CT signs or a positive VQ scan should prompt a referral for CTEPH confirmation and evaluation for treatment, including pulmonary endarterectomy. The precise interpretation and early recognition of radiographic signs of CTEPH are essential to improve outcomes.

HYPOXIC PULMONARY HYPERTENSION RESULTS IN EXPANSION OF RIGHT VENTRICULAR CCR2+ MACROPHAGES

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Category: Basic Science
Selected Areas: Diseases and Conditions Associated with PH

Background: Macrophages play critical roles in tissue homeostasis and response to disease and may provide novel therapeutic targets in right heart failure. We hypothesize that the right ventricle (RV) contains macrophage populations at steady state that orchestrate the RV adaptation to pulmonary hypertension.

Methods: C57BL/6J mice at 8–10 weeks were placed in hypobaric hypoxia at 18000 feet or in normoxia at sea level for 4 or 21 days. We measured hemodynamics, resecting the RV and left ventricle (LV), and identified populations of CCR2+ and CCR2− macrophages using flow cytometry.

Results: The RV contained a higher proportion of CCR2+ macrophages than the LV at steady state (43% versus 9.3%, $P < 0.0001$), 4-day hypoxia (37% versus 12.6%, $P = 0.0014$), and 3-week hypoxia (54.5% versus 20%, $P = 0.0007$). After 3-week hypoxia, mice developed pulmonary hypertension with RV systolic pressure of 36 mm Hg versus 24 mm Hg in normoxic mice ($P < 0.0001$) and a trend toward RV hypertrophy with increased Fulton index (0.48 versus 0.32, $P = 0.08$). Three-week hypoxic mice had significantly increased RV macrophages per milligram tissue compared with normoxic mice (224.8 versus 63, $P = 0.03$), particularly in the CCR2+ subset of macrophages (132.5 versus 31.3, $P = 0.03$; Figure).

Conclusions: The RV in homeostasis and hypoxia contains a higher proportion of CCR2+ macrophages than the LV. Chronic hypoxic pulmonary hypertension results in an expansion of all macrophages, particularly CCR2+ macrophages, in the RV which we posit play a role in RV adaptation to pulmonary hypertension.

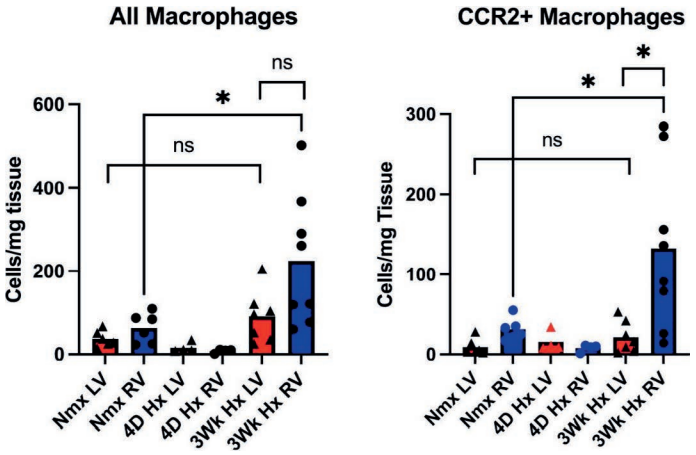

Figure 1: (**Left**) All cardiac macrophages and (**Right**) subset of CCR2+ macrophages quantified by flow cytometry. 3Wk Hx, 3-week hypoxia; 4D Hx, 4-day hypoxia; LV, left ventricle; Nmx, normoxia; RV, right ventricle.

DEFINING METHAMPHETAMINE-ASSOCIATED PULMONARY ARTERIAL HYPERTENSION IN AN ACADEMIC MEDICAL CENTER

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Category: Clinical Science
Selected Areas: Databases and Registries, Diseases and Conditions Associated with PH

Background: Methamphetamine prevalence has been increasing through the last decade and is associated with multiple cardiovascular complications, including pulmonary arterial hypertension (PAH). In this abstract, we are aiming to define methamphetamine-PAH to find out the rate of hospitalizations, mortality, and quality of life.
Methods: Investigators at the University of Utah Pulmonary Hypertension Program enrolled adults diagnosed

Table 1. Baseline Characteristics of Methamphetamine-Induced Pulmonary Arterial Hypertension Group

	Pulmonary arterial hypertension patients, n (%) (N = 67)
Age groups	
25–64	61 (91)
65–74	5 (75)
Deceased	1 (1.5)
Sex	
Male	33 (49.3)
Female	34 (50.7)
Ethnicity	
Not Hispanic or Latino	62 (92.5)
Hispanic or Latino	3 (4.5)
Unknown	2 (3)
Substance abuse history:	
Methamphetamine	55 (82.1)
Methamphetamine and heroin	5 (7.5)
Methamphetamine and cocaine	7 (10.4)
Past medical history	
HTN	25 (37.3)
Atrial fibrillation	7 (10.4)
Hyperlipidemia	17 (25.4)
Diabetes mellitus	15 (22.4)
Chronic kidney disease	9 (13.4)
COPD	9 (13.4)
CVA	1 (1.5)
Smoking	20 (29.9)
Cardiovascular medications	
B-blockers	14 (20.9)
Angiotensin converting enzyme inhibitors	7 (10.4)
Angiotensin II receptor blockers	9 (13.4)
Loop diuretics	55 (82.1)
Mineralocorticoid receptor antagonists	27 (40.3)
SGLT-2 inhibitor	4 (6)
Pulmonary arterial hypertensions medications	
Calcium channels blockers	8 (11.9)
Endothelin receptor antagonist	40 (59.7)
Phosphodiesterase-5 inhibitor	56 (83.6)
Guanylate cyclase stimulator	3 (4.5)
Prostacyclin agonist	11 (16.4)
Prostacyclin analogues	9 (13.4)

COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; HTN, hypertension.

Table 2. Hemodynamics for Methamphetamine-Induced Pulmonary Arterial Hypertension Group

Pressure	Mean	Median	Mode	Standard deviation
Right atrial pressure, mm Hg	10.4844	10.0000	7.00	5.79269
Mean pulmonary artery pressure, mm Hg	47.8788	48.5000	50.00	13.84587
Pulmonary capillary wedge pressure, mm Hg	13.8333	12.0000	12.00	6.55998
Pulmonary vascular resistance, Wood units	25.7483	8.8500	3.60	125.79573
Cardiac output, L/min/m^2	19.8244	4.4400	3.40	122.39368
Cardiac index, L/min/m^2	2.4598	2.4000	1.90	0.77376
Tricuspid annular plane systolic excursion, mm	18.9400	18.0000	18.00	5.76273
Left ventricle ejection fraction, %	64.7016	67.0000	55.00	10.84341

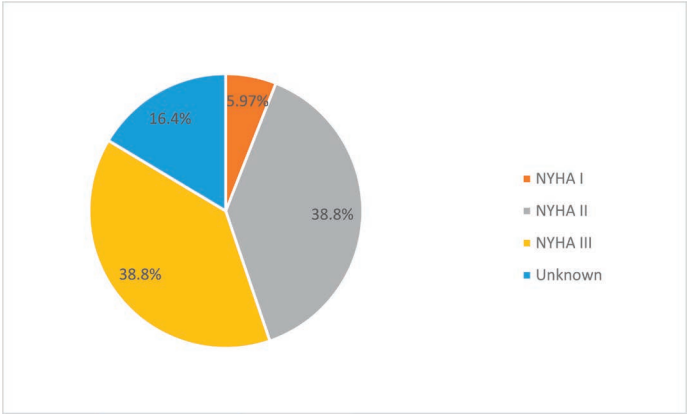

Figure 1: New York Heart Association class for methamphetamine-induced pulmonary arterial hypertension group.

with World Health Organization Group 1 PAH, toxin induced, who were seen between August 2020 and December 2021 in a program-specific registry. Their exposure histories were collected through structured interview and questionnaires, and their hemodynamic criteria were recorded. A total of 67 patients with methamphetamine-associated PAH were enrolled within the University of Utah Registry.

Results: Of the 67 patients enrolled, 50.7% were female, 91% were between the ages of 25 and 64. In 82.1% of patients, there was a history of methamphetamine use only (Table 1). The remaining 17.9% had a history of methamphetamine use and either cocaine or heroin. Most of the patients had Functional Class II–III (Figure). Hypertension was seen in 37.3%, hyperlipidemia in 25.4%, and 22.4% had a history of type 2 diabetes mellitus (Table 2).

Conclusions: In this United States Pulmonary Hypertension Association-accredited academic medical center, there are significant numbers of patients with methamphetamine-associated PAH. Published literature currently lacks large multicenter studies on methamphetamine-associated PAH and factors that affect the progression of this disease.

CONTRASTING PULMONARY ARTERIAL HYPERTENSION PHENOTYPES IN A PULMONARY HYPERTENSION ASSOCIATION-COMPREHENSIVE CARE CENTER VERSUS UNITED STATES NATIONAL REGISTRY DATA

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Category: Clinical Science
Selected Areas: Databases and Registries; Diagnosis or Screening and Physiologic Studies; Effect of COVID and Telemedicine on PH Management

Background: The phenotype of pulmonary arterial hypertension (PAH) continues to evolve. In this study, we report the characteristics of patients seen in an academic medical center for PAH from August 2020 through November 2021 and contrast those with nationally reported data.
Methods: Investigators at the University of Utah PAH center prospectively enrolled adults diagnosed with World Health Organization Group 1 PAH who were seen between August 2020 and November 2021 in a registry. A total of 251 patients were enrolled within the University of Utah PAH Registry (Table 1).
Results: Of the 251 patients enrolled, the most common etiology was associated-PAH (APAH), accounting for 72% of the population (Figure, Table 2, Table 3). The second largest etiology was idiopathic PAH (IPAH) at 26%. Of the total population with APAH, 36% of cases were noted as secondary to connective tissue disease, and 35% were toxin induced (26% and 25% of the total population, respectively). The remainder of patients were familial PAH and other subgroups of PAH. This contrasts significantly with the percentages reported by the United States Pulmonary Hypertension Registry, among others, where 51% are IPAH, and toxin-APAH accounts for only 18%. Of note, 8% of the patients enrolled in the University of Utah Registry were not on PAH-specific therapies. This contrasts with the published national registries, where nonadherence is <1%.
Conclusions: In a US academic medical center, the PAH population contrasts with traditional reported percentages of etiology of PAH. APAH,

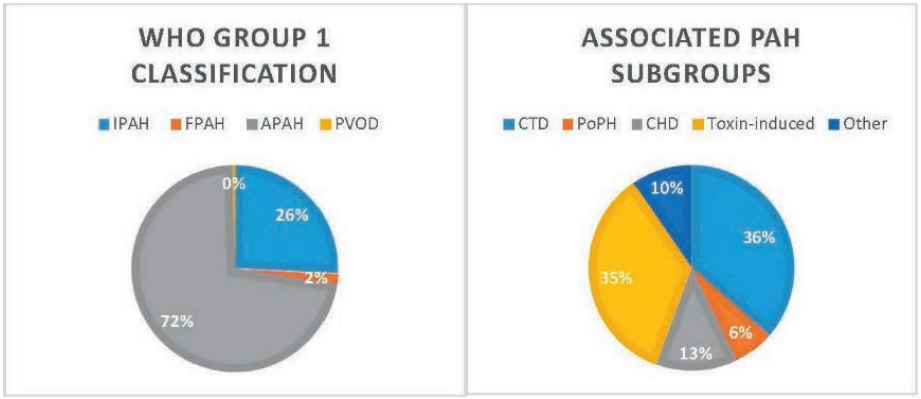

Figure 1: (**Left**) Classification of World Health Organization (WHO) Group 1 at enrollment in the University of Utah Pulmonary Arterial Hypertension (PAH) Registry based on clinical criteria. These classifications were idiopathic (IPAH), familial (FPAH), associated (APAH), and pulmonary veno-occlusive disease (PVOD). (**Right**) APAH was further classified as the following: connective tissue disease (CTD), portopulmonary hypertension (PoPH), congenital heart disease (CHD), toxin induced, and other (HHR, HIV, and hematologic malignancy).

Table 1. Total Patients Enrolled on Therapy for Pulmonary Arterial Hypertension (PAH) by Medication Class

Variable	Oral Therapy				Prostacyclin Pathway			
	CCB	PDE-5 Inhibitor	ERA	Riociguat	Selexipeg	Oral Treprostinil	Inhaled Troprostinil	Injectable Treprostinil
Overall, N=231	31 (13.4)	212 (91.8)	141 (61)	8 (3.5)	38 (16.5)	2 (0.9)	3 (1.3)	26 (11.3)
Monotherapy	0	73 (34.4)	5 (3.5)	1 (12.5)	0	0	0	0
Combination, Dual Oral Therapy (a)	0	74 (34.9)	76 (53.9)	3 (37.5)	0	0	0	0
Combination, Oral/Prostacyclin (b)	0	10 (4.7)	0	0	6 (15.8)	0	0	4 (15.4)
Combination, Triple Therapy (c)	0	55 (25.9)	60 (42.6)	4 (50)	32 (84.2)	2	3	22 (84.6)

Data are presented as n (%). CCBs were not included in combination therapy categories. Injectable treprostinil accounts for both intravenous and subcutaneous administration. (a) 2 of 3 oral therapies (ERA, PDE-5, riociguat); (b) 1 oral therapy and one prostacyclin pathway; (c) triple therapy consisting of 2 oral therapies and 1 prostacyclin pathway. CCB, calcium channel blocker (eg, amlopidine, nifedipine); ERA, endothelin receptor antagonist (eg, ambrisentan, macitentan); PDE-5 inhibitor, phosphodiesterase-5 inhibitor (eg, sildenafil, tadalafil).

Table 2. Demographic Data and Characteristics of Subjects at Time of Enrollment According to Classification

Characteristic	All Patients	IPAH	FPAH	PVOD	APAH
Patients	251	65	4	1	182
Age Group					
25-64 y	152 (60.56)	32 (49.23)	2 (50)	1 (100)	117 (64.3)
65-74 y	62 (24.7)	16 (24.6)	0	0	45 (24.7)
> 75 y	28 (11.16)	15 (23.1)	2 (50)	0	13 (7.14)
Deceased	7 (2.79)	0	0	0	7 (3.85)
Female sex	180 (71.71)	52 (80)	4 (100)	1 (100)	124 (68.13)
Race					
Asian	4 (1.59)	1 (1.54)	0	0	3 (1.65)
Black	6 (2.39)	0	0	0	6 (3.30)
Native American/Alaskan	5 (1.99)	1 (1.54)	0	0	4 (2.20)
Pacific Islander	2 (0.8)	0	1	0	1 (0.55)
White	217 (86.45)	58 (89.23)	3	1	156 (85.71)
Other	17 (6.77)	5 (7.69)	0	0	12 (6.59)
Hispanic or Latino ethnicity	19 (7.57)	7 (10.29)	0	0	12 (6.59)
BMI, kg/m²	30 ± 7.17	31.66 ± 6.76	35.36 ± 6.46	37.22	29.29 ± 7.18

Presented as % or mean ± standard deviation

not IPAH, accounts for most cases. This may reflect regional variation or practice patterns. This study is limited by the lack of genotyping.

Table 3. Diagnostic Data Including Right Heart Catheterization Hemodynamics, Functional Class, and 6-Minute Walk Distance (6MWD) at Time of Enrollment According to World Health Organization (WHO) Group 1 Classification

Characteristic	All Patients	IPAH	FPAH	PVOD	APAH
Functional class	n= 251	n = 65	n= 4	n=1	n= 182
I	11 (4.38)	3 (4.6)	0	0	8 (4.4)
II	147 (56.57)	45 (69.2)	2 (50)	0	101 (55.5)
III	62 (24.7)	12 (18.5)	1 (25)	1	51 (28)
IV	8 (3.19)	0	0	0	8 (4.4)
not available	20 (7.97)	5 (7.7)	1 (25)	0	14 (7.7)
6MWD, m	407.25 ± 136.16	388.21 ± 132.1	351.67 ± 119.54	NA	413.98 ± 137.07
N	205	56	3	0	146
mPAP, mmHg	41.32 ± 14.27	40.17 ± 13.62	46.75 ± 14.2	45	41.53 ± 14.39
N	251	65	4	1	182
PCWP, mmHg	11.13 ± 3.15	10.78 ± 2.98	13.75 ± 1.09	12	11.19 ± 3.45
N	251	65	4	1	182
mRAP, mmHg	10.61 ± 19.95	8.47 ± 8.87	10.75 ± 4.6	NA	8.78 ± 4.61
N	248	60	4	1	174
PVR, wu	4.66 ± 6.43	6.78 ± 4.44	7.83 ± 5.38	5.5	7.87 ± 6.99
N	246	62	4	1	180
CO, TD	5.18 ± 1.64	5.16 ± 1.35	5.83 ± 1.87	NA	5.19 ± 1.74
N	209	54	4	0	152
CI, TD	2.74 ± 0.79	2.64 ± 0.63	2.62 ± 2.62	NA	2.78 ± 0.85
N	199	53	4	0	143

Presented as % or mean ± standard deviation

THE ART BEHIND LINES, OPACITIES, ADENOPATHY, AND EDEMA: PULMONARY VENO-OCCLUSIVE DISEASE

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Category: Case Report
Selected Areas: Diseases and Conditions Associated with PH

Background: Pulmonary veno-occlusive disease (PVOD) is a rare cause of Group 1 pulmonary hypertension (PH) and difficult to distinguish clinically and hemodynamically from idiopathic pulmonary arterial hypertension. Therefore, we must rely on the thorax high-resolution computed tomography (THRCT) diagnostic triad and clinical cues to reach a correct diagnosis.
Methods: (Case) A 74-year-old female with history of limited scleroderma presented with dyspnea New York Heart Association (NYHA) Class IV and NT-pro-BNP of 350 pg/mL. Right heart catheterization showed: right atrial pressure = 3mmHG, pulmonary artery pressure = 78/33/48mmHG, pulmonary capillary wedge pressure = 10mmHG, cardiac index = 1.59L/min/m2, SVO_2 = 65%, and pulmonary vascular resistance = 15.9 WU. Shortly after epoprostenol infusion,

chest x ray revealed pulmonary edema. THRCT showed the radiological diagnostic triad (Figure).
Results: (Decision making) Findings of pulmonary edema after epoprostenol infusion, triad THRCT features, and limited scleroderma strongly suggested diagnosis of PVOD. Therapy was initiated with low-dose up-titration of intravenous infusion epoprostenol with a target dose of 10–12 ng/kg/min in combination with endothelin receptor antagonist macitentan. After 8 months, NT-pro-BNP reduced to 57 pg/mL, and dyspnea improved to NYHA Class III, along with quality of life.
Conclusions: This case illustrates the sensitivity of radiological features, which led to the diagnosis of PVOD, the presumptive high prevalence of PVOD in limited scleroderma, and the possible treatment response with pulmonary arterial hypertension-specific therapy in patients who are not lung transplant candidates.

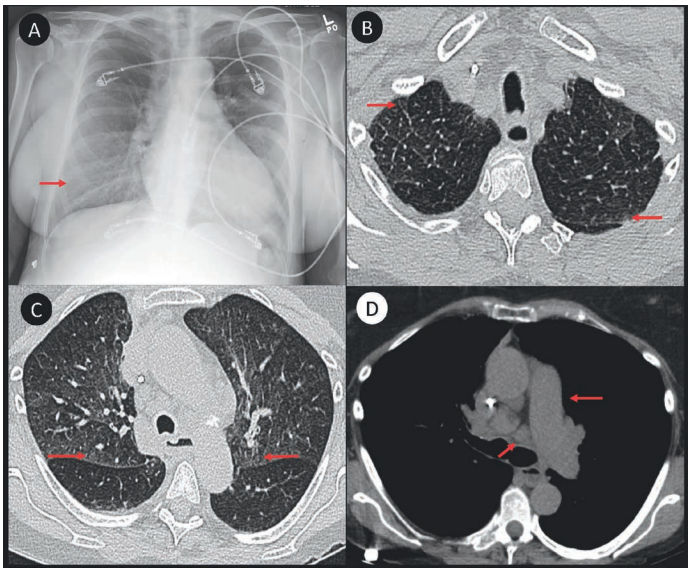

Figure 1: Radiologic diagnostic triad. (**A**) Posteroanterior chest x ray shows a prominent main pulmonary artery and Kerley B lines (arrow). (**B**) Axial high-resolution computed tomographic (CT) image of the upper lobes shows smoothly thickened interlobular septa (arrows) and geographic ground-glass opacities. (**C**) Axial high-resolution CT image shows widespread ground-glass opacities (arrows) and few septal lines. (**D**) Axial CT image (mediastinal window) shows dilated main pulmonary artery and enlarged mediastinal lymph nodes (arrows).

OUTCOMES OF EXTRACORPOREAL MEMBRANE OXYGENATOR SUPPORT IN PULMONARY HYPERTENSION PATIENT WITH COVID-19 INFECTION: MULTICENTER EXPERIENCE

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Category: Clinical Science
Selected Areas: Databases and Registries

Background: Extracorporeal membrane oxygenator (ECMO) support in adult patients diagnosed with COVID-19 infection has been widely used; however, the outcomes of this procedure in chronic pulmonary hypertension remain unknown.
Methods: A retrospective cohort study of all patients over 18 years old diagnosed with COVID-19 infection reported to the Extracorporeal Life Support Organization Registry from 2020 until 2021.
Results: A total of 7253 patients diagnosed with COVID-19 who underwent ECMO support were divided into patients without pulmonary hypertension (No-PH; 96%), patients with acute PH (acute-PH; 2%), and patients with chronic PH (chronic-PH; 2%). There were no differences on median age (No-PH = 49 years versus acute-PH = 48 years versus chronic-PH = 50 years). Chronic-PH patients had more comorbidities, such as acute renal failure (45% versus No-PH 29% versus acute-PH 29%, $P < 0.001$), liver disease (27% versus No-PH 3% versus acute-PH 4%, $P < 0.001$), and heart failure (25% versus No-PH 6% versus acute-PH 15%, $P < 0.001$). Chronic-PH patients had longer median hours on ECMO support (604 hours versus No-PH 425 hours versus acute-PH 409 hours, $P < 0.001$), and higher complications (84% versus No-PH 70% versus acute-PH 81%, $P < 0.001$). Inpatient mortality was higher in chronic-PH patients (64% versus No-PH 53% versus acute-PH 51%, $P = 0.04$). When comparing mortality cases between groups, chronic-PH patients had more liver disease (No-PH 4% versus chronic-PH 33%, $P < 0.001$, odds ratio [OR] = 12.4 [7.7–20.0]), chronic lung disease (No-PH 5% versus chronic-PH 10%, OR = 2.3 [1.1–4.6]), and heart failure (No-PH 8% versus chronic-PH 26%, $P < 0.001$, OR = 4.3 [2.6–7.1]); however, liver disease was the only factor associated with increased mortality ($P = 0.03$, OR = 2.6 [1.1–6.3]).
Conclusions: Chronic-PH patients diagnosed with COVID-19 infection undergoing ECMO support have higher comorbidities and inpatient mortality than No-PH or acute-PH patients.

USE OF LIQ861 TO IMPROVE HEALTH-RELATED QUALITY OF LIFE FOR PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION

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Category: Clinical Science
Selected Areas: Quality of Life; Therapeutic Strategies

Background: Liquidia has developed LIQ861, a dry powder formulation of treprostinil by using PRINT Technology, designed to enhance deep-lung delivery and enable QID delivery of doses in 2 breaths per capsule via a convenient, palm-sized dry powder inhaler. PRINT Technology produces drug particles that are precise in size, shape, and composition.
Methods: The INSPIRE trial was a phase 3, open-label, multicenter trial (LTI-301) that enrolled patients with pulmonary arterial hypertension (PAH) over 18 years of age who transitioned to LIQ861 from nebulized treprostinil (Transition) or added LIQ861 to 2 nonprostacyclin oral therapies, prostacyclin naïve (Naïve). The Minnesota Living With Heart Failure Questionnaire (MLHFQ) survey was administered at baseline, 2 months, and 4 months during the trial.
Results: One hundred and twenty-one patients were enrolled in the trial, including 55 in the Transition group and 66 in the Naïve group. Most patients were female, white, and non-Hispanic, with a mean age of 54.2 years. Approximately two-thirds of the patients were New York Heart Association (NYHA) Functional Classification (FC) II, the remaining being NYHA FC III. Most patients received background PAH medications, with 71% receiving a combination of endothelin receptor antagonist and phosphodiesterase 5 inhibitor or soluble guanylate cyclase agonists.
By month 4 (N = 104), there was a clinically meaningful improvement in the total MLHFQ score for all patients from baseline. Overall, the mean score of 36.0 at baseline decreased to 25.8. At month 4, both physical and emotional dimension scores decreased from 16.2 to 11.8 and 7.8 to 5.2, respectively. Improvements were seen in both the Transition and Naïve patient groups.
Conclusions: Treatment with LIQ861 may help improve health-related quality of life, which has been shown to be impaired in PAH patients.

PULMONARY HYPERTENSION IN A LIMPING CHILD: A CASE OF URGEN-C

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Category: Case Reports
Selected Areas: Diseases and Conditions Associated with PH; Pediatrics

Background: Scurvy is a rare and reversible cause of pulmonary hypertension in pediatrics with few case reports. Our case is unlike prior cases, as it also included hypothyroidism.
Methods: (Case) A 4-year-old male presented with 2 months of refusal to walk due to leg pain.
Results: Right femur magnetic resonance imaging (MRI) showed presumed osteomyelitis, yet oral antibiotics were ineffective, and thus, he underwent bone biopsy. Postoperatively, he developed acute respiratory distress and hypoxia. D-dimer was elevated, and computed tomography angiogram revealed possible pulmonary embolism or acute infection. Echocardiogram indicated severe pulmonary hypertension (tricuspid regurgitation gradient 119 Torr), presumably secondary to possible pulmonary embolism. Oxygen supplementation and anticoagulation started. Hypercoagulable workup was unremarkable. Whole-body MRI indicated osteopenia. Thyroid function tests revealed severe hypothyroidism without autoimmunity. Levothyroxine was started. Rheumatologic and infectious evaluations were unremarkable. Sildenafil was initiated with mild improvement in right ventricular (RV) pressures. Given history of limited diet of peanut butter sandwiches, vitamin C level was checked and returned undetectable. Intravenous vitamin C started. Within 3 days, RV pressure reduced to 32 Torr. Exome sequencing indicated a variant of uncertain significance in NKX2-1.
He was discharged on oral vitamin C, sildenafil, levothyroxine, and oxygen. Echocardiogram normalized 4 weeks after discharge, and oxygen was weaned. He resumed ambulation. Follow-up echocardiogram 4 weeks after weaning sildenafil off remained normal.
Conclusions: (Discussion) Severe pulmonary hypertension and hypothyroidism were reversed with supplemental vitamin C. We are not aware of other case reports of scurvy with hypothyroidism. Exome findings could be relevant.

ACUTE ONSET PULMONARY ARTERIAL HYPERTENSION IN THE POSTPARTUM PERIOD: A PHANTOM PHENOTYPE

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Category: Case Report
Selected Areas: Diagnosis or Screening and Physiologic Studies; Diseases and Conditions Associated with PH; Quality of Life

Background: Idiopathic pulmonary arterial hypertension (IPAH) is a rare entity that leads to right ventricular (RV) overload and death. Postpartum unmasking of IPAH is rarely reported in the literature but may suggest a new phenotype. We report a case of a young previously healthy female with new onset severe IPAH that was discovered 3 weeks after delivery.
Methods: (Case) A 24-year-old young mother of 4 children presented to our facility 3 weeks after uneventful vaginal delivery with severe dyspnea and syncope found to have a brain natriuretic peptide (BNP) of 2056 pg/mL and normal troponin.
Results: Echocardiogram revealed a severely dilated RV, severe tricuspid regurgitation, and septal flattening. Right heart catheterization confirmed World Health Organization (WHO) Group 1 PAH with high-risk features. Parenteral prostacyclin therapy was initiated immediately. Endothelin receptor antagonist (ERA) and tadalafil was added later sequentially at various times. Acute onset PAH was followed by rapid improvement as well. She was switched to oral treprostinil after 17 months of parenteral therapy. Currently, she remains in a low-risk status—WHO Functional Class 1 after >72 months of prescription (Table).
Conclusions: This case illustrates a phenotype of PAH characterized by acute onset followed by rapid improvement with aggressive upfront treatment measures.

Table 1. Right Heart Cath, Labs, Functional Class, and Reveal Risk scores for the patient over time

	TIME OF PAH DIAGNOSIS	6 MONTHS AFTER DIAGNOSIS PRIOR TO TRANSITION ONTO ORAL TREPROSTINIL *	72 MONTHS AFTER DIAGNOSIS (ON TRIPLE COMBO THERAPY**)
mRAP (mmHg)	8	8	2
mPAP (mmHg)	67	45	28
PCWP (mmHg)	10	13	16
PVR (WU'S)	28	5.2	1.0
CO (L/MIN)	1.92	6.17	8.08
CI (L/MIN/M2)	1.14	3.55	4.38
BNP (pg/mL)	2,056	15	18
6MWT (METERS)		467	500
WHO FX CLASS	IV	I-II	I
REVEAL RISK (2.0)	13 (High)	1.0 (Low)	1.0 (Low)

*On subcutaneous treprostinil 46 ng/kg/min and ambrisentan 10 mg PO QD.

**On oral treprostinil 8 mg TID, tadalafil 40 mg QD, and ambrisentan 10 mg PO QD.

ACUTE CORONARY SYNDROME IN PULMONARY ARTERIAL HYPERTENSION—A PRESSING ISSUE

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Category: Clinical Science
Selected Areas: Diagnosis or Screening and Physiologic Studies; Diseases and Conditions Associated with PH

Background: Atrial septal defect (ASD) with Eisenmenger's physiology (EP) is classified as World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH). Pulmonary artery (PA) dilation in this setting can cause left main coronary artery (LMCA) compression and myocardial ischemia. We report a case of a 35-year-old female with ASD who had PAH decompensation secondary to myocardial infarction (MI) from LMCA compression.
Methods: (Case) A 35-year-old woman with WHO Group 1 PAH secondary to ASD and EP presented with abdominal pain and shortness of breath and was found to have acute sepsis from pelvic inflammatory disease on initial presentation.
Results: Troponin was 61 ng/mL with anterolateral T-wave inversion on electrocardiogram. Acute coronary syndrome was diagnosed, and therapeutic heparin was started. Brain natriuretic peptide was 2287 pg/mL with echocardiogram showing

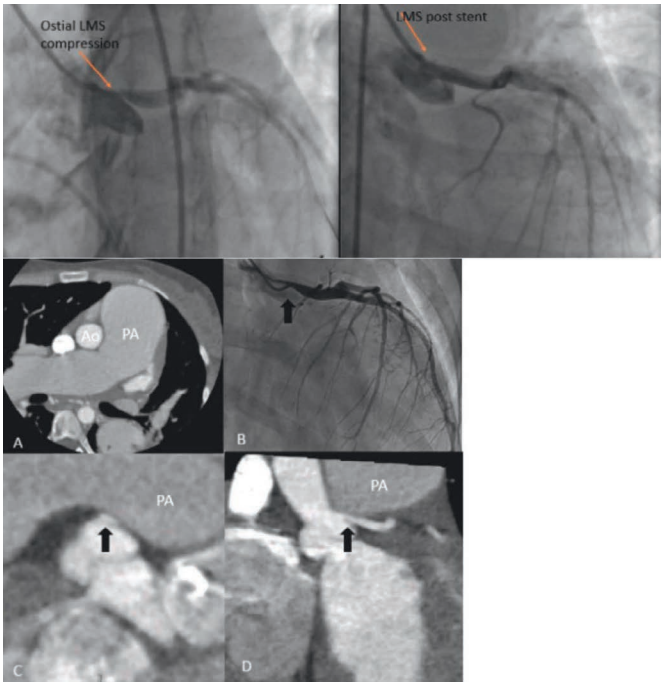

Figure 1: Cardiac imaging for (**Top left**) ostial compression of the left main stem (LMS) coronary artery by the dilated pulmonary artery (PA). (**Top right**) Image after stent placement. (**A**) Dilated PA. Ao, aorta. (**B**) Coronary angiogram showing severe LMS stenosis (arrow). (**C**) Coronary computed tomography (CT) angiogram showing severe stenosis with slitlike opening of the ostial LMS (seen in short axis, arrow). (**D**) Oblique view showing large PA compressing the ostial LMS (arrow).

preserved ejection fraction, right ventricular systolic pressure of 70 mm Hg, and septal flattening. Computed tomography pulmonary angiogram showed external LMCA compression by the PA (Figure). Coronary angiogram confirmed 95% stenosis of the LMCA without angiographic evidence of atherosclerosis. Right heart catheterization revealed mean pulmonary artery pressure of 54 mm Hg, pulmonary arterial systolic pressure of 102 mm Hg, pulmonary capillary wedge pressure of 15 mm Hg, and pulmonary vascular resistance of 4.3 Wood units. Percutaneous intervention with stent placement resulted in resolution of stenosis.

Conclusions: Sepsis can increase myocardial demand which may worsen right heart function and result in PAH decompensation. Dilatation of main PA predisposes to LMCA compression causing myocardial ischemia. Prompt recognition and intervention resulted in a positive outcome.

PLAIN LANGUAGE SUMMARY OF THE INCREASE STUDY: USING INHALED TREPROSTINIL FOR TREATING PULMONARY HYPERTENSION AND INTERSTITIAL LUNG DISEASE

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Category: Clinical Science
Selected Areas: Diseases and Conditions Associated with PH

Background: The goal of the INCREASE study was to see if inhaled treprostinil could help people with pulmonary hypertension and interstitial lung disease (PH-ILD). Before INCREASE, there was no Food and Drug Administration-approved drug for treating PH-ILD. The goal of this plain language summary is to explain the INCREASE trial so that nondoctors can understand the results.

Methods: This was a multicenter, randomized, double-blind, placebo-controlled clinical trial that lasted 16 weeks. A total of 326 people with PH-ILD took part in the study; 163 were given inhaled treprostinil (Tyvaso), and 163 were given a placebo that does not contain any medicine. Because PH-ILD causes breathing problems and tiredness, researchers wanted to test if taking inhaled treprostinil would help people with

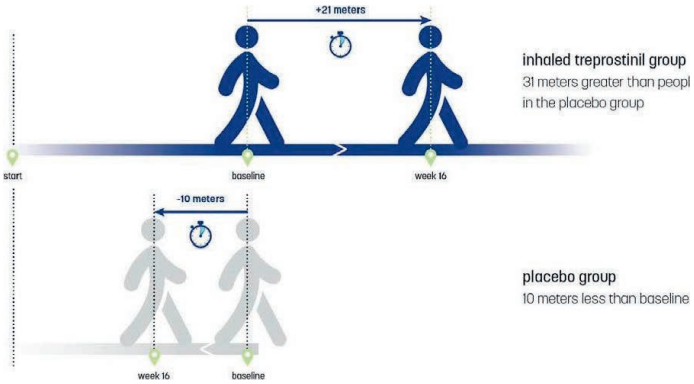

Figure 1: After 16 weeks in the study, participants taking inhaled treprostinil walked farther in 6 minutes than participants taking the placebo. At week 16, on average, participants in the inhaled treprostinil group walked 21 meters further than they did at the beginning of the study. Overall, participants in the inhaled treprostinil group had an average change from the baseline in 6-minute walk distance (6MWD) that was 31 meters (about 102 feet) greater than participants in the placebo group.

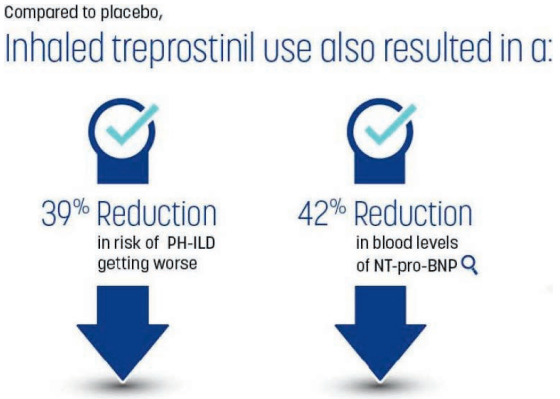

Figure 2: Study participants taking oral treprostinil showed improved clinical measurements, specifically, a reduced risk of pulmonary hypertension and interstitial lung disease (PH-ILD) getting worse and lowered NT-pro-BNP levels. Compared with participants taking the placebo, those taking inhaled treprostinil had a 39% reduced risk of their PH-ILD getting worse. NT-pro-BNP is a protein marker of heart function that can be measured with a blood test. NT-pro-BNP levels that are higher can mean that a person has heart problems. Compared with participants taking the placebo, those taking inhaled treprostinil lowered their NT-pro-BNP levels from the beginning of the study by 42%.

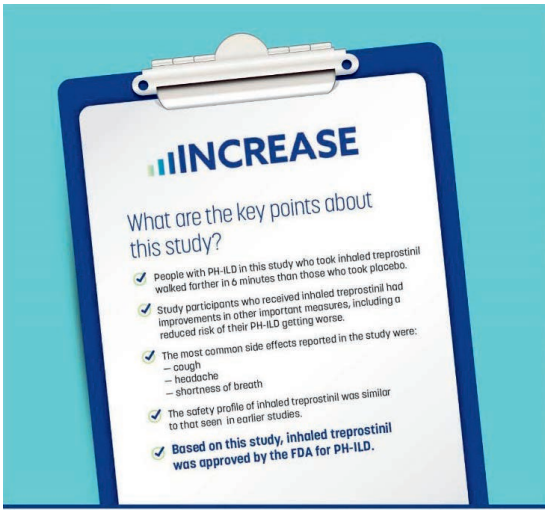

Figure 3: Summary of the INCREASE study results. For complete results, see Waxman et al. Inhaled treprostinil in pulmonary hypertension due to interstitial lung disease. *N Eng J Med*. 2021;384(4):325–334. doi:.10.1056/NEJMoa2008470.

Table 1. Side Effects Reported by >10% of Participants in Either Group During the Study

Side Effect	Participants receiving inhaled treprostinil number, (percentage)	Participants receiving placebo number, (percentage)
Cough	71 (43.6%)	54 (33.1%)
Headache	45 (27.6%)	32 (19.6%)
Shortness of breath (dyspnea)	41 (25.2%)	51 (31.3%)
Dizziness	30(18.4%)	23 (14.1%)
Nausea	25 (15.3%)	26 (16%)
Fatigue	23 (14.1%)	23 (14.1%)
Diarrhea	22 (13.5%)	19 (11.7%)
Throat irritation	20 (12.3%)	6 (3.7%)
Throat (oropharyngeal) pain	18 (11%)	4 (2.5%)

Cough, headache, and throat pain were reported more often by participants taking inhaled treprostinil than those taking the placebo.

PH-ILD walk farther in 6 minutes than people with PH-ILD taking placebo.

Results: On average, after 16 weeks in the study, people taking inhaled treprostinil raised their 6-minute walking distance by 31 meters (about 102 feet) more than people in the placebo group (Figure 1). NT-pro-BNP is a protein measuring heart function. Participants taking inhaled treprostinil lowered (improved) their NT-pro-BNP levels from the study start by 42% versus placebo (Figure 2). Compared with placebo, participants taking inhaled treprostinil had a 39% reduced risk of their PH-ILD getting worse. Cough, headache, and throat pain were reported more often by people taking inhaled treprostinil than by people taking placebo (Figure 3; Table).

Conclusions: People with PH-ILD in this study who took inhaled treprostinil walked farther in 6 minutes than those who took placebo. Study participants who received inhaled treprostinil improved other important measures, including a reduced risk of their PH-ILD getting worse.

Cough, headache, and throat pain were reported more often by participants taking inhaled treprostinil than those taking the placebo.

YOUNG WOMAN FIGHTING TWO DEMONS

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Category: Clinical Science
Selected Areas: Diagnosis or Screening and Physiologic Studies; Diseases and Conditions Associated with PH; Quality of Life

Background: Pulmonary arterial hypertension (PAH) is a devastating disease caused by remodeling of precapillary arterioles leading to a progressive increase in pulmonary vascular resistance, right heart failure, and death. Breast cancer also is a serious diagnosis associated with an adverse prognosis. We describe the case of a young woman who was diagnosed with both conditions in a brief time span. PAH was optimized with parenteral prostacyclin therapy, and she underwent successful surgical mastectomy.
Methods: (Case) A 35-year-old female was diagnosed with World Health Organization Group 1 idiopathic PAH (IPAH) with high-risk features (Table).
Results: Treatment regimen included treprostinil (SQ) and tadalafil. Shortly after, a right breast lump was detected. Evaluation revealed stage IIIb invasive ductal carcinoma with axillary lymph node (LN) involvement. Surgical mastectomy was rendered necessary despite her heightened mortality risk due to PAH. Following multidisciplinary (Surgical Oncology, Cardiac Anesthesiology, Palliative Care, and Pulmonary Hypertension teams) discussion of risks and benefits with the patient, surgery was planned. Preoperative optimization of PAH included increase in treprostinil dose and conversion to intravenous, aggressive diuresis, and pulmonary artery catheter placement. Mastectomy with axillary LN dissection was successfully completed without complication.
Conclusions: Against all odds, this young woman is fighting two serious disease processes associated with high mortality. The above case illustrates her first success. However, the road ahead is less known. A multidisciplinary approach, patient education, and hope are essential to maximize improved outcomes.

Table 1. Right Heart Catheterization Data and Brain Natriuretic Peptide

	TIME OF DIAGNOSIS	PRE-OP* (17 MONTHS AFTER DIAGNOSIS)
mRAP (mmHg)	14	4
PAP (mmHg)	66	43
PCWP (mmHg)	6	3
PVR (WU'S)	28.7	10.36
CO (L/MIN)	2.16	3.86
CI (L/MIN/M^2)	1.2	2.4
BNP	741	29
REVEAL RISK	10 (high)	8 (intermediate)

*On intravenous treprostinil 81.9 ng/kg/min.

PULMONARY HYPERTENSION ASSOCIATED WITH PARTIAL ANOMALOUS PULMONARY VENOUS RETURN

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Category: Case Report
Selected Areas: Diseases and Conditions Associated with PH; Therapeutic Strategies

Background: Partial anomalous pulmonary venous return (PAPVR) is rare congenital condition that may present during late adulthood or can go undiagnosed for years. We present 3 patients with pulmonary arterial hypertension (PAH) secondary to PAPVR whose symptoms improved after treatment.
Methods: Retrospective chart review and case series.
Results: A 60-year-old male presented with dyspnea. Echocardiogram revealed ejection fraction (EF) of 45%–50% and pulmonary arterial systolic pressure (PASP) of 83 mm Hg. Right heart catheterization (RHC) revealed PAH with pulmonary arterial pressure (PAP) of 80/40 mm Hg, and pulmonary capillary wedge pressure (PCWP) of 18 mm Hg. Computed tomography (CT) angiogram of the heart showed anomalous pulmonary venous return from the right lung. Patient was initiated on PDE-5 inhibitor with improvement in his symptoms.

A 73-year-old male presented with dyspnea. Echocardiogram revealed EF of 60% and PASP of 90 mm Hg. RHC revealed severe PAH with mean PAP of 65 mm Hg and PCWP of 26 mm Hg. Serial O_2 saturation showed a significant increase in O_2 saturation, particularly at high right atrium (RA), and superior vena cava junction of 86%. CT angiogram of the heart showed anomalous return of the left upper pulmonary vein to the superior vena cava. Patient began PDE-5 inhibitor treatment with good symptomatic response.
A 75-year-old female presented with dyspnea. Echocardiogram revealed EF of 55% and PASP of 50 mm Hg. Bubble study was positive for a right to left shunt via both arm access with a shunt ratio of 4.7. CT angiogram of the heart showed anomalous drainage of the right-sided pulmonic veins into the RA. RHC revealed PAP of 76/17 mm Hg and PCWP of 18 with a pulmonary angiogram, which demonstrated right upper, middle pulmonary veins draining into RA. Patient began PDE-5 inhibitor with improvement in her symptoms.
Conclusions: Patients with unexplained PAH should have a high degree of suspicion for PAPVR. Awareness of PAPVR is important because untreated PAPVR can lead to PAH.

SAFETY AND EFFICACY OF TRANSITIONING FROM PARENTERAL PROSTACYCLIN ANALOGS TO ORAL PROSTACYCLIN AGONIST AND THE EFFECT ON QUALITY OF LIFE

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Category: Case Report
Selected Areas: Diseases and Conditions Associated with PH; Quality of Life; Therapeutic Strategies

Background: Parenteral prostacyclin therapy is well established for patients with World Health Organization Group 1 pulmonary arterial hypertension (PAH). However, difficulty tolerating long-term parenteral therapy due to line- and delivery-related complications is common, resulting in poor quality of life. While case series describing the transition from parenteral prostacyclin to selexipag exist, there is no standardized protocol. Furthermore, we sought to assess the change in quality of life associated with the transition.
Methods: This case series includes 3 transitions (2 inpatient and 1 outpatient) from parenteral prostacyclins to selexipag between February 2020 and November 2021. Protocols are shown in Figures 1–3. Quality of life was assessed using the emPHasis-10 score.
Results: Patient 1 is a 50-year-old female with PAH and sarcoidosis on macitentan and intravenous (IV) epoprostenol, who transitioned over 7 days as an inpatient for recurrent line infections. Patient 2 is a 22-year-old female with idiopathic PAH on macitentan, sildenafil, and IV treprostinil, who transitioned over 5 days as an inpatient for recurrent line infections. Patient 3 is a 71-year-old female with HIV-associated PAH on macitentan and SQ treprostinil who had a prolonged outpatient transition for severe site discomfort. This transition over 647 days was interrupted by the COVID-19 pandemic. Mean emPHasis-10 scores decreased from 28.3 (pretransition) to 15.3 (posttransition). Six-minute walk distance (6MWD) improved, while the New York Heart Association (NYHA) Functional Class remained stable pretransition and posttransition (Table).

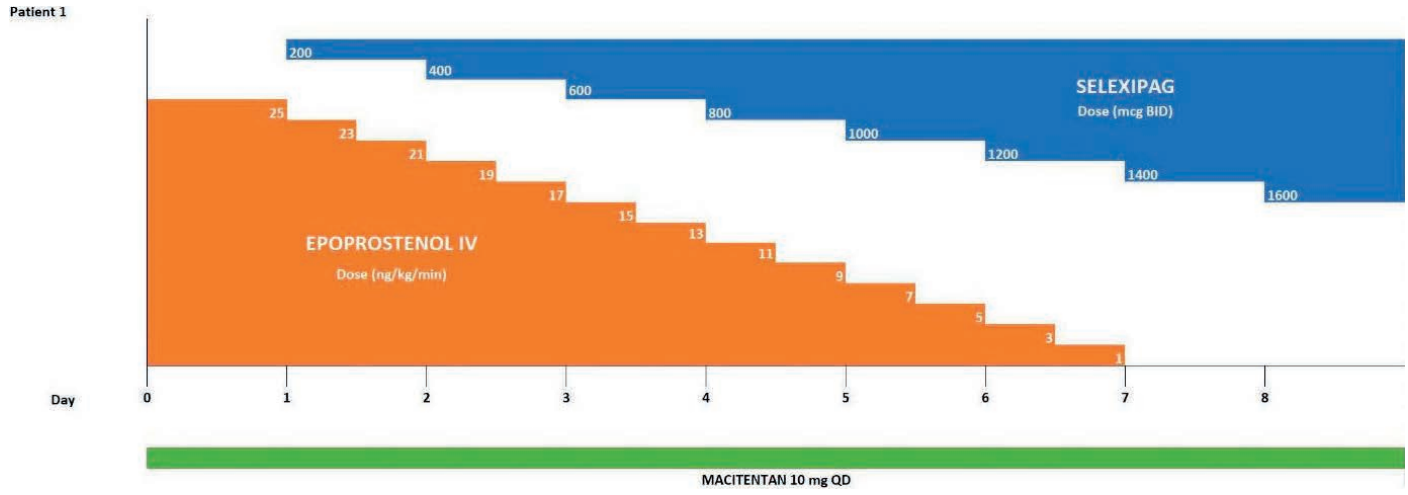

Figure 1: Protocols used for parenteral prostacyclin to selexipag transitions for Patient 1.

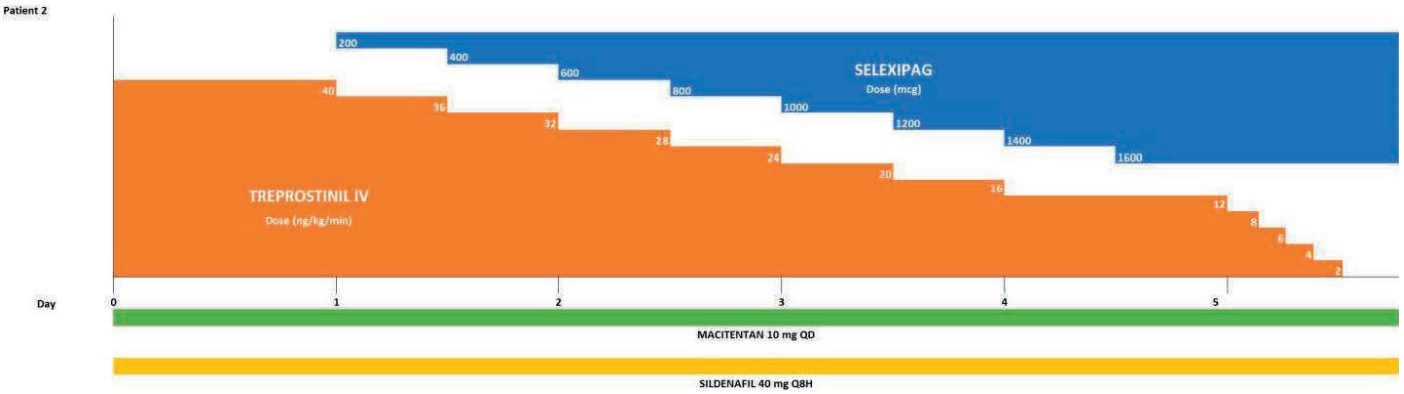

Figure 2: Protocols used for parenteral prostacyclin to selexipag transitions for Patient 2.

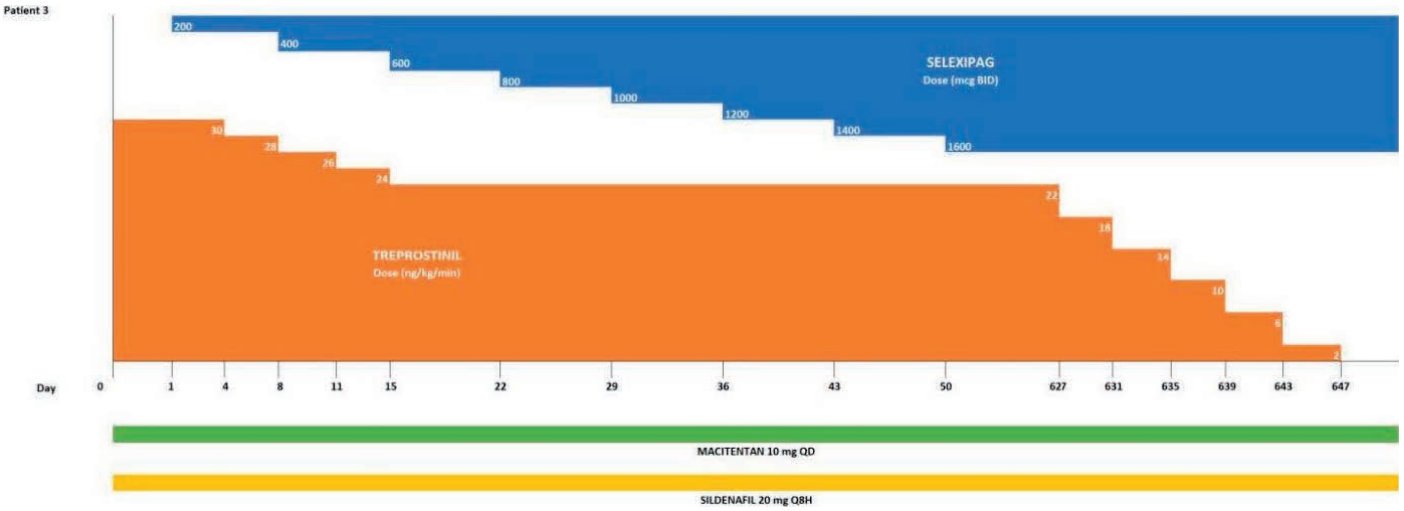

Figure 3: Protocols used for parenteral prostacyclin to selexipag transitions for Patient 3.

Table 1. Patient Demographics and Quality of Life, 6-Minute Walk Distance (6MWD), and Echocardiogram Findings

				Parenteral Prostacyclin		Selexipag		6MWD		Echocardiogram Findings		emPHasis-10 Score		NYHA Functional Class	
Patient	Age	Diagnosis	Transition	Duration on Prior to Transition	Dose at Time of Transition	Final Dose	Reason for Transition	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	50	Sarcoidosis and Group 1 PAH	IV epoprostenol to PO selexipag	36 months	23 ng/kg/min	1600 mcg BID	Line related infections	226 meters	284 meters	TAPSE: 1.8 cm RA Area: 12.2 cm^2	TAPSE: pending RA Area: pending	37	27	2	2
2	22	Idiopathic PAH	IV treprostinil to PO selexipag	19 months	36 ng/kg/min	1600 mcg BID	Line related infections, patient preference	610 meters	624 meters	TAPSE: 2.04 cm RA Area: 12.5 cm^2	TAPSE: 2.1 cm RA Area: 13 cm^2	32	8	1	1
3	71	HIV-associated PAH	SQ treprostinil to PO selexipag	13 months	30 ng/kg/min	1600 mcg BID	Severe site discomfort	190 meters	248 meters	TAPSE: 1.8 cm RA Area: 22.1 cm^2	TAPSE: 1.9 cm RA Area: 11.5 cm^2	16	11	2	2

Conclusions: Our case series provides a reference with timelines for transitioning from low-dose parenteral prostacyclins to selexipag. Patients had significant improvements in quality of life and 6MWD.

PULMONARY HYPERTENSION ASSOCIATED WITH COR TRIATRIATUM

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Category: Case Report
Selected Areas: Diseases and Conditions Associated with PH

Background: Cor triatriatum sinister is a rare congenital heart defect in which a fibromuscular membrane subdivides the left atrium (LA) into 2 chambers. We present a case report of pulmonary arterial hypertension (PAH) secondary to cor triatriatum.
Methods: Retrospective chart review and case report.
Results: A 43-year-old male presented for dyspnea on exertion. Echocardiogram showed ejection fraction of 60%, right ventricular pressure overload, pulmonary arterial systolic pressure of 80 mm Hg, and membrane separating LA chambers concerning cor triatriatum. Computed tomography (CT) angiogram of the heart showed dilated pulmonary artery (PA; 4 cm), enlarged and septated LA with evidence for cor triatriatum. Right heart catheterization (RHC) revealed severe PAH with pulmonary arterial pressure (PAP) of 95/65 mm Hg with mean of 75 mm Hg, transpulmonary gradient of 70, cardiac output was 4.65, cardiac input of 2.4. He underwent complete repair of the cor triatriatum with surgical resection of the membranes. Post-surgery repeat echocardiogram showed improved right-sided pressures, and RHC showed PAP of 62/37 with a mean of 47 mm Hg. Symptoms improved significantly after surgery.
Conclusions: Awareness of cor triatriatum is important because untreated cor triatriatum can lead to PAH. Identification of cor triatriatum sinister is increasing due to widespread use of advanced techniques, such as CT and angiography. Cor triatriatum is amenable to surgical repair with good outcomes when diagnosed early.

PAUSE AT YOUR OWN PERIL: REBOUND PULMONARY HYPERTENSION

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Category: Case Report
Selected Areas: Therapeutic Strategies

Background: After initiation of combination therapy, one must be careful about potential interruption in therapy resulting in rebound pulmonary arterial hypertension (PAH).
Methods: The first case involved a 41-year-old woman with heritable pulmonary hypertension (PH) on ambrisentan, tadalafil, and inhaled treprostinil. Given her acute cholecystitis, she was unable to tolerate her medications. The second case involved a 55-year-old woman with PAH on intravenous treprostinil and macitentan. She was without infusion for 50 minutes.
Results: Both patients experienced right heart failure and required aggressive diuresis. The first patient's echocardiogram showed a severely dilated right ventricle (RV) and right atrium (RA; 90.1 mL/m), moderate tricuspid regurgitation (TR V Max, 4.88 m/s; tricuspid annular plane systolic excursion (TAPSE), 1 cm) and RV systolic pressure of 110 mm Hg (Figure 1). The second patient's computed tomography of the thorax showed a dilated pulmonary artery (PA; Figure 2). Right heart catheterization showed RA pressure of 6 mm Hg, RV pressure of 74/10, PA pressures of 73/25, pulmonary capillary wedge pressure of 10 mm Hg, cardiac output/cardiac input of 2.4/1.6, and pulmonary vascular resistance of 15 consistent with severe precapillary PH. She was started on tadalafil.
Conclusions: Despite the vast benefits PGI2 analogues provide, careful consideration should be taken before starting them given their difficulty to discontinue. Those with poor functional class or abnormal hemodynamics have greater difficulty discontinuing from a PGI2 analogue. If discontinuation of the medication is <4–5 half-lives of the last dose taken, then the medication should be taken at the last tolerated dose. If the time between doses is >4–5 half-lives, then a lower dose with rapid up-titration based on tolerance is required (Narechania S, Torbic H, Tonelli

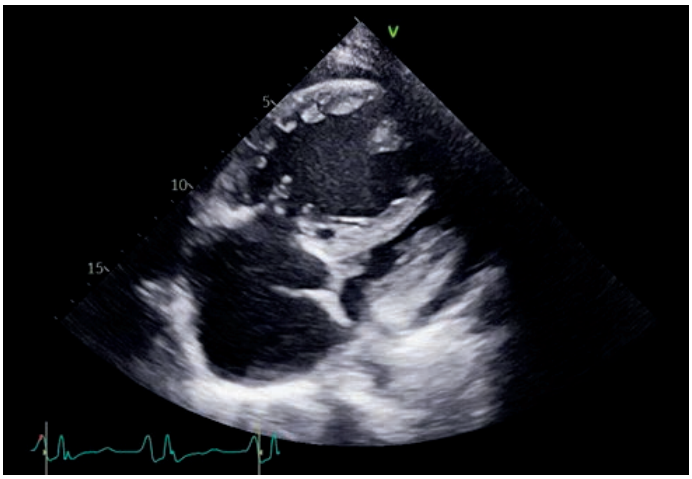

Figure 1: Echocardiogram of the first patient showing severely dilated right ventricle and right atrium.

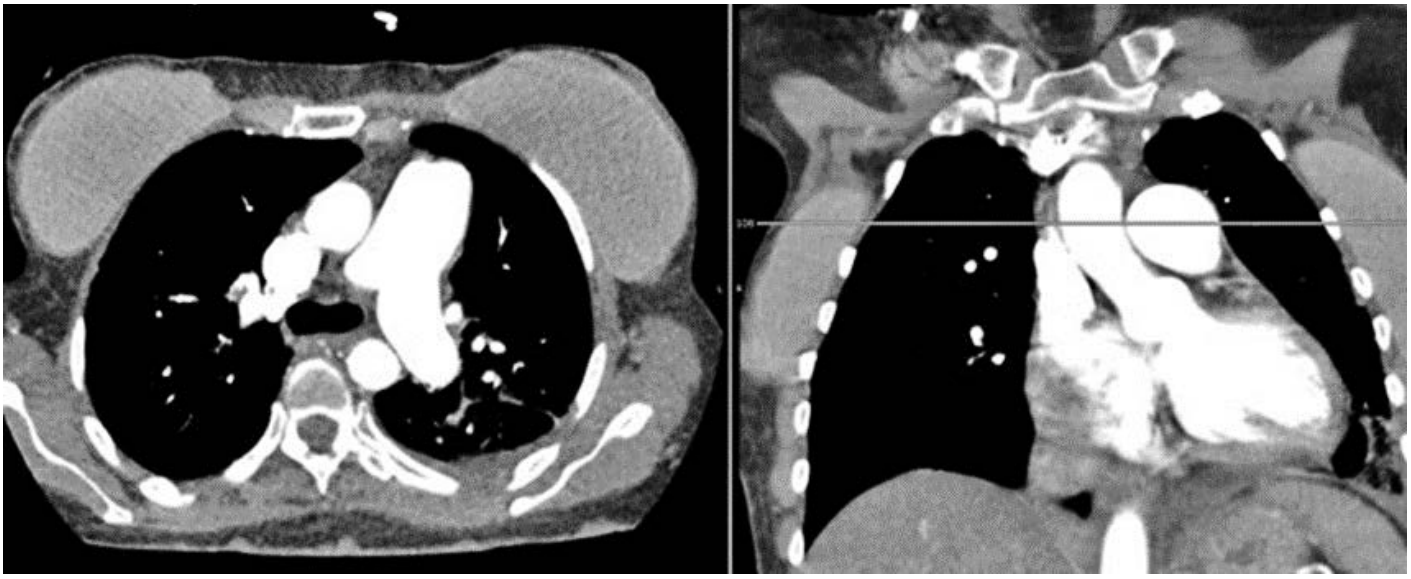

Figure 2: Computed tomography of the thorax of the second patient showing a markedly dilated pulmonary artery in comparison to the aorta.

AR. Treatment discontinuation or interruption in pulmonary arterial hypertension. *J Cardiovasc Pharmacol Ther*. 2019;25(2): 131-141. https://doi.org/10.1177/1074248419877740). These case reports highlight the importance and severity of abrupt discontinuation of PAH medication and in turn provide some guidance on how to manage such patients.

MALE SEX IS ASSOCIATED WITH DECREASED RIGHT VENTRICULAR FUNCTION AND SURVIVAL IN GROUP 1–5 PULMONARY HYPERTENSION

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PVDOMICS Study Group

Category: Clinical Science
Selected Areas: Diagnosis or Screening and Physiologic Studies

Background: Sex-based differences are important factors in the development and progression of PH. We sought to use the deep phenotyping of the PVDOMICS project to test the hypothesis that males with pulmonary hypertension (PH) will have worse right ventricular (RV) function than females at similar elevations of pulmonary vascular resistance (PVR).

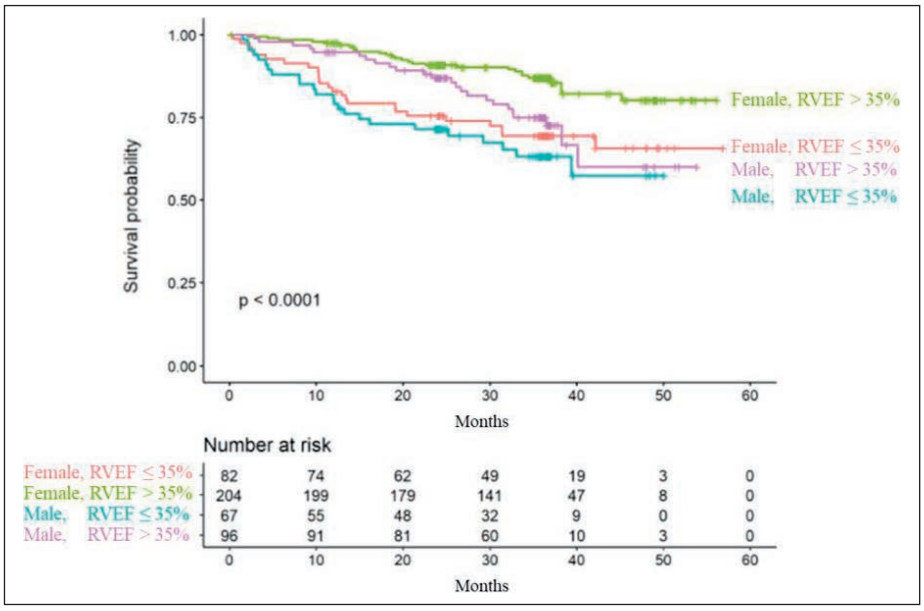

Figure 1: (**Top**) Kaplan-Meier curve for transplant-free survival by sex and (**Bottom**) number at risk based on the presence or absence of right ventricular dysfunction on cardiac magnetic resonance imaging (defined by RVEF = 35%).

Methods: Subjects enrolled in PVDOMICS with PH were included. For this analysis, subjects were grouped based on PVR: 2.4–5 and >5 Wood units (WU), and differences in RV ejection fraction (EF) on cardiac magnetic resonance imaging between men and women were assessed using the Wilcoxon rank sum test. Effects of sex and RV function on transplant-free survival were assessed using Cox Proportional Hazards Model.
Results: A total of 750 patients with PH (62.8% female) were enrolled. World Symposia on Pulmonary Hypertension Group 1 patients were most predominantly female at 73.4%. Among the 349 PH patients (61.8% female) with measurements of both RVEF and PVR, RVEF was significantly lower in men (38.3 ± 10.2% versus 42.4 ± 11.8%, $P < 0.001$), while there was no significant difference in PVR (5.4 ± 3.4 versus 5.9 ± 3.8 WU, $P = 0.3$). In PH patients with mild elevation in PVR (2.4–5 WU; n = 148, 58.8% female), RVEF was reduced in men (41.0 ± 9.3% versus 46.8 ± 10.3%, $P < 0.001$); however, in patients with PVR >5 WU (n = 157, 64.3% female), the trend toward worsened RVEF in men was not significant (34.3 ± 9.8% versus 37.3 ± 11.5%, $P = 0.09$). In PH patients, female sex was associated with improved survival (heart rate = 0.61, 95% confidence interval = 0.46–0.82), and this difference was partially mediated by differences in RVEF (natural indirect effect: -0.14, $P = 0.01$; Figure).
Conclusions: Among PH patients with mild elevations in PVR, RV function is significantly worse in men. Women with PH have improved survival compared with men, and this difference is partially explained by differences in RV function.

FEASIBILITY OF INTRAVENOUS TO ORAL HOME TRANSITIONS WITH PROSTACYCLIN THERAPY IN PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION DURING THE COVID-19 ERA

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Category: Case Report
Selected Areas: Effect of COVID and Telemedicine on PH Management; Quality of Life; Therapeutic Strategies

Background: During the COVID-19 pandemic, there was a need for providers to continue providing quality care for pulmonary arterial hypertension (PAH) patients despite limitations in access to care. Safe transitions of PAH patients from intravenous (IV) prostacyclin therapy to PO selexipag therapy in the inpatient setting have previously been described in several case series with mixed results, but there is a dearth of experience with the outpatient setting.

Methods: In this case series, we describe the successful transition of 4 patients with World Health Organization (WHO) Group 1 PAH and WHO Functional Class (FC) 1 or 2 symptoms who were transitioned at home under supervision of the PAH team. We compared the differences in their baseline and follow-up functional class, 6-minute walk distance, echocardiograms, right heart catheterizations, and reported quality of life.
Results: Patients were all female (2 Caucasian, 2 African American) with an age range of 26–54 years. The primary reasons for transitioning patients to PO therapy were to improve quality of life and unmanageable IV prostacyclin side effects. The length of IV therapy prior to PO transition ranged from 3 to 100 months with an epoprostenol maintenance dose range of 9–29.5 ng/kg/min. Three out of the 4 patients were on triple PAH therapy. Patients were transitioned with an average decrement of epoprostenol of 0.62 ng/kg/min/day and an average weekly increase of selexipag of 172 mcg twice daily over a range of 17–57 days. There were no significant changes in FC nor significant complications related to PAH in the first 3 months following transition. All patients reported an improvement in their quality of life.
Conclusions: Home IV to PO therapy transitions can be done successfully in carefully selected patients with guidance from a multidisciplinary team.

RODATRISTAT ETHYL, A TRYPTOPHAN HYDROXYLASE INHIBITOR IN PHASE 2B FOR PAH DEMONSTRATES LOW POTENTIAL FOR AFFECTING BRAIN SEROTONIN BIOSYNTHESIS

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Category: Basic Science
Selected Areas: Diseases and Conditions Associated with PH

Background: Rodatristat (R), as rodatristat ethyl (RE) prodrug, inhibits tryptophan hydroxylase (TPH) the rate-limiting enzyme in serotonin (5-HT) biosynthesis. In pulmonary arterial hypertension (PAH), elevated 5-HT in pulmonary endothelial cells drives vascular remodeling. Key to TPH therapy is avoiding reductions in brain 5-HT. Here, we leverage nonclinical disposition data, with mood and Columbia-Suicide Severity Rating Scale (C-SSRS) assessments in healthy subjects, to assess potential for central nervous system effects.
Methods: Potency for TPH inhibition, protein binding, and blood-brain barrier passage were measured in vitro. Tissue disposition was by quantitative whole-body autoradiography in rats receiving 14C-RE at the dose efficacious in rat PAH models. Rat brain 5-HT was measured after 21 days RE at 2× the efficacious dose. In healthy subjects, C-SSRS data were collected at baseline and after 14 days of either: 400 mg BID, 800 mg BID, 500 mg QD, or 800 mg QD RE.
Results: In vitro R potently inhibits nonneuronal TPH1 (IC50, 52 nM) and neuronal TPH2 (9 nM); however, exposure was barely detectable in rat brain consistent with in vitro data (>99% protein bound; permeability <25 nm/s). Brain 5-HT was unaffected in monocarboxylate transporter (MCT) + vehicle and MCT + RE animals. Free R levels in lung were ~3× the TPH1 IC50, yielding robust reductions in tissue 5-HT in MCT rats. Plasma concentration (Cmax) for R was ~2560 ng/mL. In healthy subjects, steady-state Cmax was 1370 ng/mL (800 mg BID RE) and 1260 ng/mL (600 mg BID, highest phase 2b dose). Plasma concentrations in humans are ~50% of rat where no changes in brain 5-HT were observed. In humans, there were no changes in mood or suicidal ideation in any subject across all dose groups (n = 36).
Conclusions: RE should not affect brain 5-HT nor mood in humans.

GROWTH DIFFERENTIATION FACTOR 15 IS ASSOCIATED WITH INCREASED PULMONARY ARTERIAL HYPERTENSION SEVERITY AND DECREASED SURVIVAL

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Category: Clinical Science
Selected Areas: Diagnosis or Screening and Physiologic Studies

Background: Pulmonary arterial hypertension (PAH) is a progressive disease characterized by vascular remodeling resulting in right ventricular pressure overload and right heart failure. Growth differentiation factor 15 (GDF-15), a member of the transforming growth factor-B cytokine superfamily, is a

left heart failure biomarker with pilot evidence of elevation in patients with PAH.
Rationale: Determine diagnostic and prognostic utility of GDF-15 levels in PAH patients via correlation with deteriorating clinical severity and mortality rates.
Methods: Serum GDF-15 levels from the National Heart, Lung, and Blood Institute PAH Biobank were evaluated by enzyme-linked immunosorbent assay (ELISA). A total of 1932 subjects and 50 healthy controls was evaluated. Association of GDF-15 levels with PAH clinical variables were assessed via Spearman's rank correlation test and Kruskal-Wallis test. Cox multivariable and Kaplan-Meier analyses were used to examine survival associations with GDF-15.
Results: Receiver operating characteristic (ROC) analysis evaluated GDF-15's ability to distinguish between PAH and controls with area under the curve = 0.85. By PAH classification, connective tissue participants had highest overall GDF-15 levels (3.07 ± 2.5 ng/mL). Higher GDF-15 correlated with higher New York Heart Association Classification. Adjusted GDF-15 levels were associated with a 20 m decrease in 6-minute walk distance (95% confidence interval [CI] = −29.2 to −11.3, $P < 0.001$), and a 0.58 mm Hg increase in right atrial pressure (95% CI = 0.29–0.86, $P < 0.001$). Kaplan-Meier analyses showed a significant difference in survival curves and adjusted Cox proportional hazards showed a 1.88 greater risk of death (95% CI = 1.59–2.23, $P < 0.001$; Figure).
Conclusions: Measuring GDF-15 levels may offer additional prognostic value in the clinical evaluation of PAH.

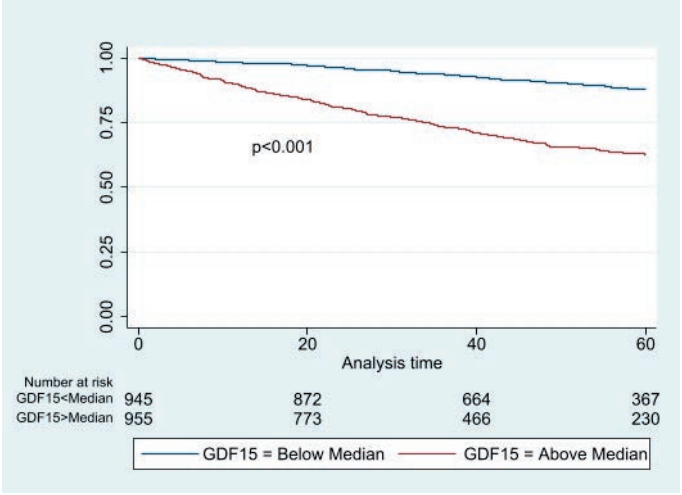

Figure 1: GDF-15 Kaplan-Meier survival estimates.

MULTIDISCIPLINARY CARE TEAM INTEGRATION: THE BASIS OF A SUCCESSFUL PEDIATRIC PULMONARY HYPERTENSION CARE CENTER

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Category: Clinical Science
Selected Areas: Pediatrics

Background: Multidisciplinary care teams (MDTs) work jointly to implement patient care interventions to meet the complex needs of individuals with chronic illnesses. Pediatric pulmonary hypertension (PH) is specifically associated with significant morbidity and mortality, putting children at high risk of clinical deterioration.
Methods: A MDT care team model was adapted to meet the needs of our large pediatric PH population of >300 patients, infants to 21 years of age. This care team model was separated into 2 major clinical care settings of the PH patient: outpatient and inpatient. To target specific care concerns within these 2 clinical care settings, MDT activities were established. To improve outpatient MDT involvement, an outpatient huddle was structured and preanesthesia recommendation documentation was created. Weekly team inpatient rounds, multidisciplinary rounds, and integration of a discharge checklist were targeted at improving inpatient MDT care team involvement.
Results: There are many strengths associated with the MDT care model in the PH population. These strengths include improved collaboration among various specialties to work jointly to meet the needs of the patient and family, reduction of patient safety errors, and increased team member satisfaction. Weaknesses include a need for clearly defined roles in the team and frequent collaboration via meetings.
Conclusions: The complexities of the pediatric PH population are best matched with the expertise of an experienced MDT team. Adapting a MDT care team model that integrates various activities to optimize the care of the pediatric PH patient in the inpatient and outpatient settings ensures time for collaboration.

COMPREHENSIVE CARDIAC SCREENING CAMPS IN RESOURCE-LIMITED SETTINGS CAN BREAK THE ICEBERG PHENOMENA IN PULMONARY HYPERTENSION

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Category: Clinical Science
Selected Areas: Diagnosis or Screening and Physiologic Studies

Background: Pulmonary hypertension (PH), defined by mean pulmonary arterial pressure = 25 mm Hg at rest, that is related with congenital heart disease is usually known as congenital heart disease associated with pulmonary arterial hypertension (CHD-APAH). Undiagnosed congenital heart defects such as septal defect, subaortic stenosis, and mitral valve prolapse are rare. However, in a resource-limited rural setting with a lack of diagnostic awareness and services like echocardiograms or cardiac catheterization, they are likely to go unnoticed or be diagnosed late and with complications. Hence, we proposed implementing comprehensive cardiac screening camps in these settings to diagnose CHD-APAH, which would otherwise have gone unnoticed.
Methods: Pulmonary Hypertension Association Nepal, together with local health officials and cardiac specialists, implemented health screening camps at several elementary and middle schools in 4 rural villages in Nepal. We did comprehensive cardiac screening of 1383 children (mean age = 11 ± 3 years) by conducting interviews on cardiac-related clinical features and risk factors as well as doing 4–6-minute walk tests, detailed physical examinations of heart and lung conditions.
Results: Here, 21% of those evaluated had an abnormal heart sound. Thirty-two suspected cases were referred and evaluated in tertiary centers using echocardiogram and catheterization. Of these, 18 were suffering from mild to moderate CHD, and 8 were diagnosed to be suffering from CHD-APAH.
Conclusions: Comprehensive screening in a resource-limited setting via an outreach camp is a novel method to break the iceberg phenomenon in PH and may prevent PH-associated disability and early mortality.

EFFECT OF PEDIATRIC COVID-19 VACCINATION IMPLEMENTATION ON INFLUENZA VACCINATION RATES AMONG CHILDREN WITH PULMONARY HYPERTENSION

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Category: Clinical Science
Selected Areas: Databases and Registries; Effect of COVID and Telemedicine on PH Management; Pediatrics

Background: Over the past several decades, caregivers have expressed increasing concern over the safety and efficacy of pediatric vaccinations. In 2021, the US Food and Drug Administration (FDA) authorized the emergency use of the Pfizer-BioNTech COVID-19 Vaccine (CV) for the prevention of COVID-19 in children 5–18 years of age. However, the administration of the CV in the pediatric population triggered considerable controversy that exposed and created significant parental hesitation over vaccinations in general. Immunization reluctance was of particular concern in the pediatric pulmonary hypertension (PH) population due to high risk for negative sequelae from infections such as influenza. We hypothesized that caregiver concerns regarding CVs would decrease vaccination rates for influenza vaccine in the pediatric PH population.
Methods: This was a single-center, retrospective study of vaccination rates for COVID-19 and seasonal influenza in children with PH, ages 5–18 years. Vaccination rates were tracked from August 2021 to March 2022 (2021 flu season, during the pandemic; Figures 1 and 2) and compared with August 2019 to March 2021 (2019 flu season, prepandemic). Data were obtained from the hospital's electronic medical record, Epic (Wiscon-

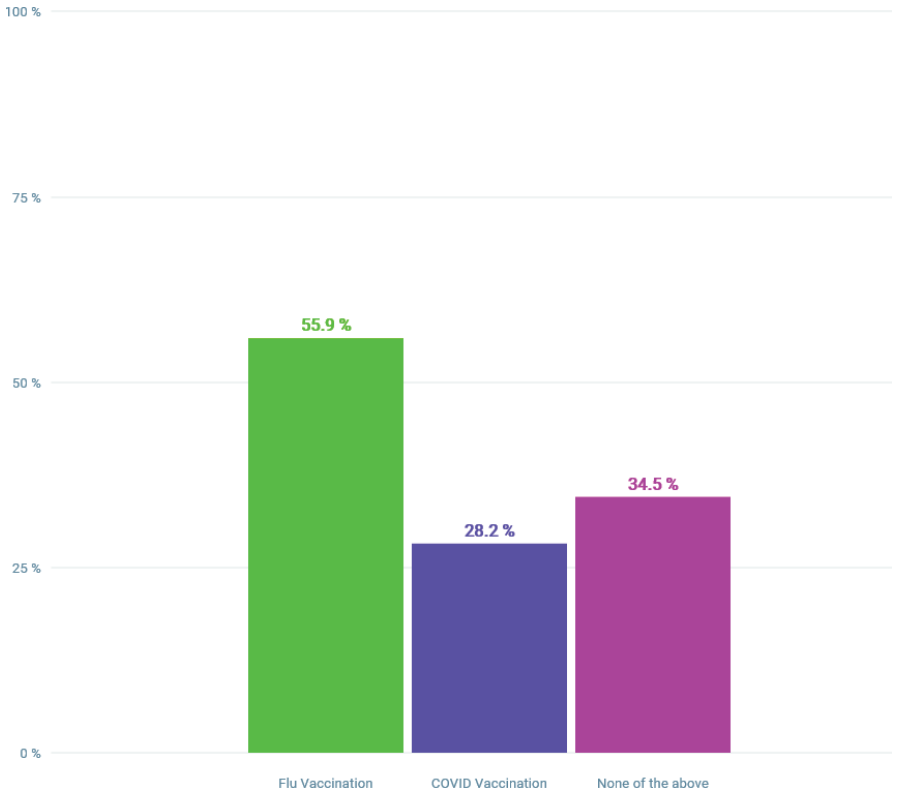

Figure 1: Percentage of population by immunizations (between August 1, 2021, and March 1, 2022).

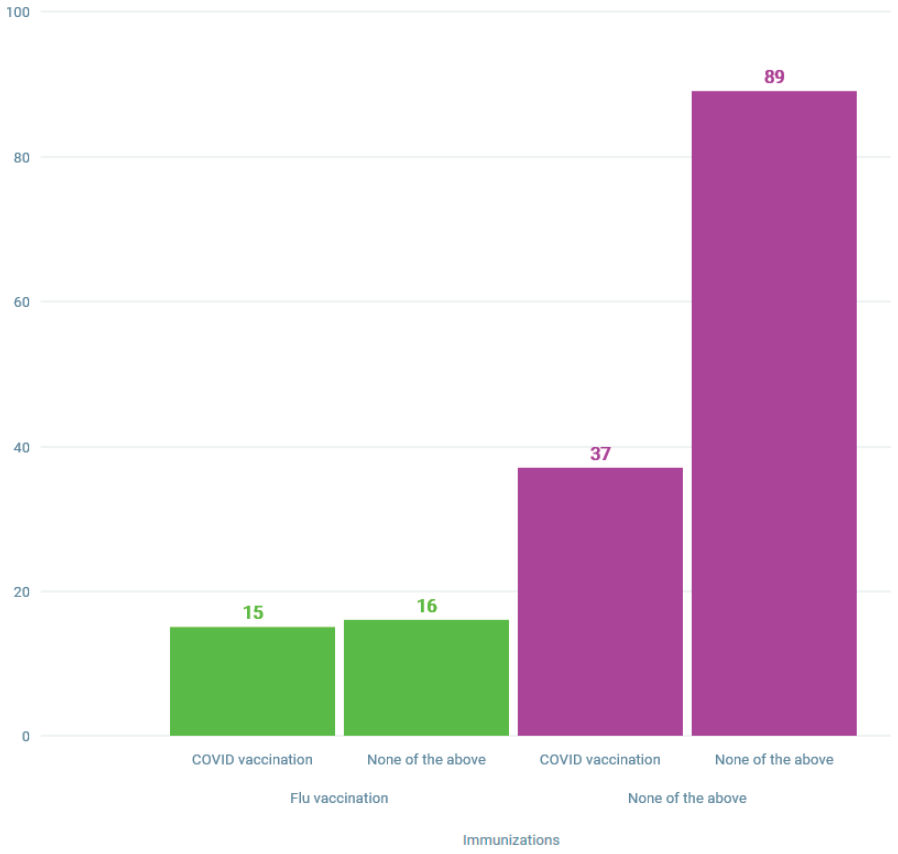

Figure 2: Number of patients by immunizations and immunization types (between August 1, 2021, and March 1, 2022).

sin, May 2021). Institutional review board approval was obtained.

Results: During the study period, 295 children actively received care at our PH Center. One hundred fifty-seven patients were between the ages of 5 and 18 year. During the 2021 influenza season, 31 children received the flu vaccine (20%), 37 children received the CV (24%), and 15 children received both flu vaccine and CV (10%). In comparison, during the 2019 influenza season, 37 children received the flu vaccine (24%; Figure 3). Community burden of influenza infection in the 5–18-year-old age group during these periods was 3% in the 2019 season and <1% in the 2021 season.

Conclusions: In this single-center study, rates of influenza vaccination did not vary greatly between prepandemic and pandemic periods. Controversies around CV for children did not seem to affect rates of influenza vaccination among our patients. Overall, the influenza vaccination rates in our pediatric PH population were low, suggesting opportunity for a dedicated quality improvement project to address vaccination rates in our clinic.

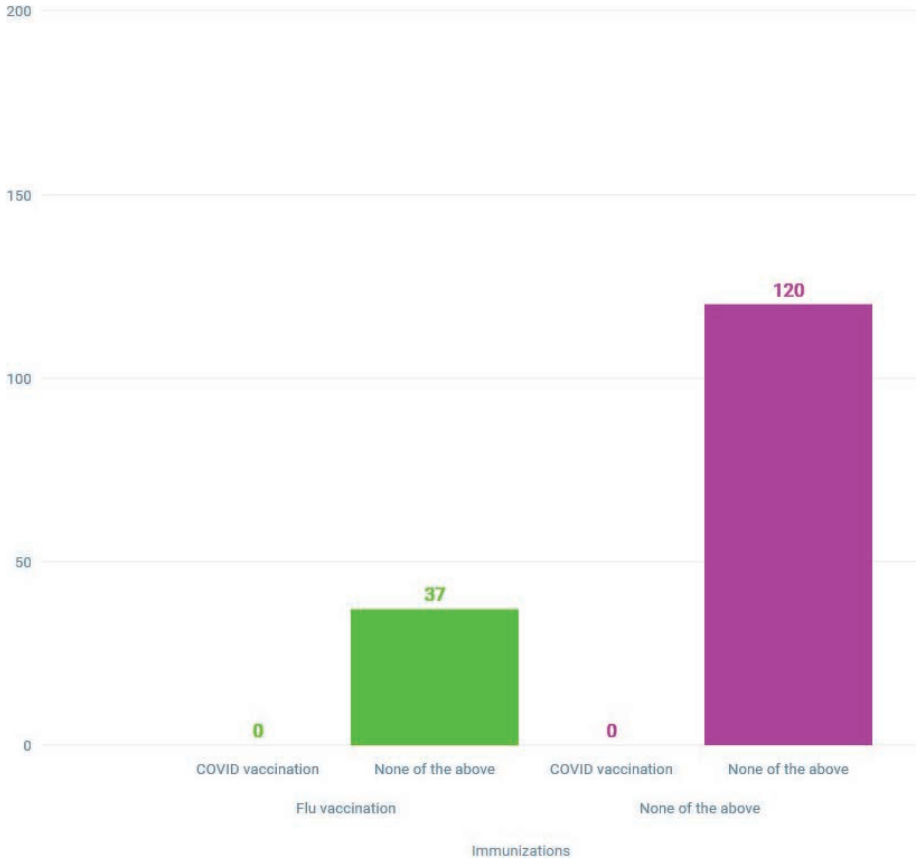

Figure 3: Number of patients by immunizations and immunization types (between August 1, 2019, and March 1, 2020).